National Library of Canada
Acquisitions and Bibliographic Services Branch
395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale du Canada
Direction des acquisitions et des services bibliographiques
395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file - Votre référence

Our file - Notre référence

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

UNIVERSITY OF ALBERTA

DIURNAL PATTERN OF RUNNING IN ACTIVITY ANOREXIA: THE ANIMAL MODEL

©

by

ALLEN D. MORSE

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

EXPERIMENTAL SURGERY
DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

SPRING 1994

National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

L'auteur a accordé une licence irrévocable et non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de sa thèse de quelque manière et sous quelque forme que ce soit pour mettre des exemplaires de cette thèse à la disposition des personnes intéressées.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

L'auteur conserve la propriété du droit d'auteur qui protège sa thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

ISBN 0-612-11292-6

Canada

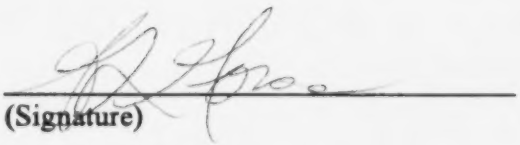
UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR:	Allen D. Morse
TITLE OF THESIS:	Diurnal Pattern of Running in Activity Anorexia: The Animal Model
DEGREE:	Master of Science
YEAR THIS DEGREE GRANTED:	1994

Permission is hereby granted to the University of Alberta Library to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly, or scientific research purposes only.

The author reserves all other publication and other rights in association with the copyright in the thesis, and, except as hereinbefore provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatever without the author's prior written permission.



(Signature)

Permanent Address:

11107 - 21 Avenue
Edmonton, Alberta T6J 5C7
Canada

December 17, 1993

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled, *Diurnal Pattern of Running in Activity Anorexia: The Animal Model,* submitted by Allen D. Morse in partial fulfillment of the requirements for the degree of Master of Science in Experimental Surgery.

Dr. J. C. Russell, Supervisor

Dr. W. F. Epling

Dr. W. D. Pierce

December 17, 1993

To the memory of my father, David L. Morse

ABSTRACT

Activity anorexia is characterized by a marked decrease in food consumption and a distinct increase in physical activity (exercise). An analogous state can be induced in rats through mild food restriction and manipulation. Food restriction is accomplished by the manipulation of two parameters: duration and size of the meal. Rats restricted to a daily 90-minute meal period and given access to a running wheel exhibit rapidly increasing levels of physical activity and decreasing food consumption. This process results in an increasingly unstable condition that is ultimately not compatible with life. Concurrent with the physical decompensation, rats in this condition also exhibited an abnormal diurnal cycle of activity. While rats are normally nocturnal, wheel running in these rats occurred throughout the light and dark periods. Rats restricted in meal size to 15 g of food per day also showed increasing levels of wheel running activity. Such rats consistently ran 14,000 m/day, with a biphasic pattern of wheel running activity that was confined to the dark phase of the circadian cycle. In contrast, wheel running activity of rats on an ad libitum feeding schedule occurred in short bursts, confined to the dark phase. These rats consistently ran 3,500 m/day. A new computer monitoring device designed specifically for these experiments allowed for the quantitative unobtrusive incremental recording of the diurnal pattern of activity of rats in different food-restricted conditions. The precise analysis thus achieved has

revealed a complexity and sensitivity in the behavioral patterns of rats that have not heretofore been recognized.

Acknowledgements

This thesis could never have been completed without the valuable encouragement and consistent support of my wife, Miriam, who has endured many rodent-centred conversations over the past years. I also wish to thank Sandy, Juno, and Louise for their technical support and encouragement.

In addition, I wish to express my gratitude to my committee members, Drs. Epling and Pierce, for their helpful direction. Particular thanks to Dr. Jim Russell, who provided lab space, animals, and countless hours of instruction without which there would have been no worthwhile endeavour.

TABLE OF CONTENTS

Page

I. Introduction

1. Introduction 1
2. References 4

II. Measurement of Diurnal Variation of Running Activity in Rats

1. Introduction 6
2. Methods 8
3. Results 12
4. Discussion 13
5. References 21

III. Diurnal Pattern of Wheel Running Activity in the Rat: Effects of Food Deprivation in Activity Anorexia

1. Introduction 23
2. Methods 24
3. Results 28
4. Discussion 31
5. References 43

IV. General Discussion

1. Introduction 47
2. History 47
3. Modern Perspectives on Activity Anorexia 49
4. Conclusion 70
5. References 72

LIST OF FIGURES

Page

Fig. 2-1. Schematic arrangement of connections between the microswitches on the running wheels and the computer. The functions illustrated are incorporated into the logic circuit device 16

Fig. 2-2. A typical raw data file collected with the Data Capture Program, showing hourly collection of running data from 8 rats 17

Fig. 2-3. Diurnal pattern of running in freely fed rats. The animals were weighed daily at 1800 hrs and provided with food in excess of their daily consumption. The data were collected at 15-minute intervals and represent the mean activity of 10 rats over 2 days (20 observations per point). The line is a splined curve fitted to the data. The dark horizontal line indicates the period of darkness, and the arrow, the time of feeding 18

Fig. 2-4. Diurnal pattern of running in the steady state running protocol described in the text. The rats were weighed and fed 18 g of food at 1800 hrs. Other details are as in Fig. 2.2 19

Fig. 2-5. Diurnal pattern of running in which rats were freely fed and weighed during the light cycle (2000 hrs). Data were collected hourly and represent the mean activity of 5 rats over 4 days (20 observations per point). The line is a splined curve fitted to the data 20

Fig. 3-1. Average wheel running activity as a function of food supply in free food (n = 10), 15 g/day (n = 9), and 90-minute conditions (n = 9) 36

Fig. 3-2. Average body weight of all rats in free food (n = 10), 15 g/day (n = 9), and 90-minute conditions (n = 9). 37

Fig. 3-3. Average food consumed by all rats in free food, 15 g/day, and 90-minute conditions. 38

Page

Fig. 3-4. Diurnal variation in wheel running under free food condition, Day 4. Data represent the mean running of 10 rats in 15-minute intervals. Vertical bars indicate standard error of the mean. The arrow indicates time of day at which the rats were fed 39

Fig. 3-5. Diurnal variation in wheel running under restricted food (15 g/day), Day 4. Data represent the mean running of 9 rats in 15-minute intervals. Vertical bars indicate standard error of the mean. The arrow indicates time of day at which the rats were fed 40

Fig. 3-6. Diurnal variation in wheel running for the first 96 hours under the 90-minute condition. Data represent the mean running of 9 rats in 15-minute intervals. The arrow indicates time of day at which the rats were fed 41

Fig. 3-7. Diurnal variation in wheel running under the 90-minute meal condition, Day 4. Data represent the mean running of 9 rats in 15-minute intervals. Vertical bars indicate standard error of the mean 42

Chapter 1:

INTRODUCTION

Anorectic behavior, commonly called "anorexia nervosa," has been recognized for hundreds of years (Gull, 1874; Lasèque, 1873; Morton, 1694). The syndrome is characterized by chaotic dieting and excessive exercise that result in peripheral and central physiological abnormalities that pose a serious health hazard to otherwise healthy adolescents and young adults.

The *Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM-III-R) (1987) classifies anorexia nervosa as a psychiatric disorder that is primarily characterized by distorted thought processes, fears of gaining weight, and refusal to maintain body weight. However, hyperactivity was also recognized as component of the syndrome as early as 1873 (Gull, 1874). Recently, Epling and co-workers presented a view that emphasized environmental and physiological determinants of a process they called activity anorexia (Epling, Pierce & Stefan, 1983). In their view, anorectic behavior is a normal response to abnormal environmental conditions. It is defined as a cyclic sequence of events initiated by food restriction and results in excessive physical exercise. Increased physical exercise further reduces food intake, eventually resulting in self-starvation.

The hyperactivity reported in humans who have been diagnosed with anorexia nervosa is strikingly similar to the physical activity exhibited by food-

restricted rats (Katz, 1986). Rats will exhibit anorectic behavior when moderately food deprived and allowed access to a running wheel (Epling et al., 1983; Routtenberg & Kuznesof, 1967; Russell, Epling, Pierce, Amy & Boer, 1987). Under normal conditions, rats given free access to a running wheel and ad libitum food will consume 22-25 g/day and run 3,500 m/day (Boer, 1989). Rats given free access to a running wheel and restricted to a 90-minute meal once a day, rats will run excessively to the exclusion of eating. These animals show a substantial reduction in body weight, and die if the process is allowed to continue. In contrast, sedentary animals given the same food restriction adapt to the feeding schedule and eventually regain their body weight. Animals maintained on free access to food and given the oppertunity to run on exercise wheels also adapt to this condition (Epling & Pierce, 1984). Later work demonstrated that the provision of a fixed amount of food once a day induced a less severe physical activity that could be stabilized through the control of daily food allocation (Russell et al., 1987). This protocol induced stable running activity in excess of 10,000 m/day for periods of many months (Russell et al., 1987).

In previous studies, 24-hour totals of rat running activity were recorded using commercially available rodent running wheels fitted with mechanical or electrical turn counters. Problems that can arise with the use of these counters include: partial turns of the wheel counted as complete turns, missed counts and

totals that have to be manually read (Boer, Epling, Pierce & Russell, 1989; Epling et al., 1984; Russell et al., 1987). As well, stimulation caused by direct reading of these counters in the vicinity of the rats may disturb their wheel running patterns (Teghtsoonian & Campbell, 1960). Because of this interference, only a limited number of readings are possible and practical during any 24-hour period. Previous studies have also employed remote event recording (Peng & Kang, 1984; Stewart, Rosenwasser & Adler, 1985) or computer-based turn counting (Stephan, 1983). However, these techniques do not permit unambiguous recordings of complete wheel turns nor the precise continuous incremental collection of wheel turn data. The development of a new computer-based data collection technique (Morse, Wood, Hunt & Russell, 1993) enables a precise quantitative analysis of the diurnal pattern of wheel running behavior exhibited by rats food restricted by size or duration of meal.

References

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised). Washington, DC: Author.

Boer, D. P. (1989). *Determinants of Excessive Running in Activity Anorexia.* Unpublished doctoral dissertation, University of Alberta, Alberta.

Boer, D. P., Epling, W. F., Pierce, W. D., & Russell, J. C. (1989). Suppression of food deprivation-induced high-rate wheel running in rats. *Physiology and Behavior* **48**: 339-342.

Epling, W. F., Pierce, W. D., & Stefan, L. (1983). A theory of activity-based anorexia. *International Journal of Eating Disorders* **3**: 27-46.

Epling, W. F., & Pierce, W. D. (1991). *Solving the Anorexia Puzzle: A Scientific Approach.* Toronto: Hagrefe and Haber.

Gull, W. (1874). Anorexia nervosa (apepsia) hysteria, anorexia hysteria. *Transcripts of the Clinical Society, London* **7**:22-31.

Katz, J. L. (1986). Long-distance running, anorexia nervosa, and bulimia. *Comprehensive Psychiatry* **27**(1):74-78.

Laseque, C. (1873). On hysterical anorexia. *Medical Times and Gazette* **2**: 265-266, 367-369.

Morse, A. D., Hunt, T., Wood, G. O., & Russell, J. C. (1993). Measurement of diurnal variation of running activity in rats. *Physiology and Behavior* (submitted for publication).

Morton, R. (1694). *Phthisiologica: Or a Treatise of Consumptions*. London: Smith and Walford.

Peng, M. T., & Kang, M. (1984). Circadian rhythm and patterns of running-wheel activity, feeding and drinking behaviors of old male rats. *Physiology and Behavior* **33**: 615-620.

Routtenberg, A., & Kuznesof, A. W. (1967). Self-starvation in rats living in activity wheels on a restricted feeding schedule. *Journal of Comparative and Physiological Psychology* **64**(3): 414-421.

Russell, J. C., Epling, W. F., Pierce, W. D., Amy, R., & Boer, D. P. (1987). Induction of voluntary prolonged running by rats. *Journal of Applied Physiology* **63**: 2549-2553.

Stephan, F. K. (1983). Circadian rhythms in the rat: Constant darkness, entrainment to T cycles and to skeleton photoperiods. *Physiology and Behavior* **30**: 451-462.

Stewart, K. T., Rosenwasser, A. M., & Adler, N. T. (1985). Interactions between nocturnal feeding and wheel running patterns in the rat. *Physiology and Behavior* **34**: 601-608.

Teghtsoonian, R., & Campbell, B. A. (1960). Random activity of the rat during food deprivation as a function of environmental conditions. *Journal of Comparative and Physiological Psychology* **53**(3): 242-244.

Chapter 2:

MEASUREMENT OF DIURNAL VARIATION OF RUNNING ACTIVITY IN THE RAT

INTRODUCTION

If young rats are restricted to 90 minutes access to food each day, they will adapt and eat sufficient food to survive in good health. However, if a running wheel is made available and food is restricted, the rats will begin to run. The distance run increases rapidly day by day, food consumption during the 90-minute access period decreases, and the rat begins to lose weight. This process leads to physical decompensation, and running may exceed 15,000 m/day while food consumption decreases to 1 g/day or less, a situation that is not compatible with life (Epling, Pierce & Stefan, 1983). This experimental protocol provides a animal model for the human activity anorexia (Epling & Pierce, 1985; Epling et al., 1983). The unstable wheel running can be stabilized by a small procedural change: the provision of a fixed amount of food each day that is adjusted in response to running (Russell, Epling, Pierce, Amy & Boer, 1987). Initially, 15 g of food (*vs* 22-25 g/day normal consumption) is provided each day to 6-week-old rats. This food restriction results in a linear increase in running. When wheel running reaches 8,000 m/day, it can be stabilized through

---

A version of this chapter has been submitted for publication. Morse, Hunt, Wood & Russell, 1993. *Physiology and Behavior.*

the provision of 18 g of food per day. This steady state running has been shown to be inhibited by the opiate antagonist, naloxone (Boer, Epling, Pierce & Russell, 1990). The decrease in the daily distance run was not large, but the effect was significant, indicating that endogenous opioids play a role in the maintenance of the excessive activity.

Since the rat is a nocturnal animal, running activity occurs largely during the dark phase. However, the diurnal cycle of running behavior in this animal is complex, with multiple peaks of activity occurring in the dark phase (Peng & Kang, 1984; Stephan, 1983). This behavior pattern has been found to be highly sensitive to disturbance.

Earlier studies measuring rat running behavior have in general relied on commercially available rodent running wheels that are fitted with simple mechanical or electrical turn counters. Problems can arise in that these devices can falsely count partial turns of the wheel as complete turns and in that only a limited number of readings are practical during any given day. Of greater importance, since these counters must be read manually, direct readings in the vicinity of the animals creates a significant disturbance of their behavioral pattern. Other investigators have used remote event recording (Peng & Kang, 1984; Stewart, Rosenwasser & Adler, 1985) or computer-based turn counting (Stephan, 1983); however, these techniques did not permit unambiguous detection of complete wheel turns or quantitative data for precise analysis.

These problems and the need for efficient data collection and manipulation have led us to develop a computer-based recording technique that gives a detailed recording of actual wheel revolutions and permits direct analysis of the stored raw data. It is also readily adaptable to any behavioral study which relies on the opening or closing of an electrical switch. We have used the equipment described here to obtain detailed measurement of the time dependence and diurnal variation of running by rats exhibiting the process of activity anorexia and to illustrate the complexity and sensitivity of behavioral patterns in the rat.

METHODS

Apparatus:

Rat running wheels of 1.1 m in circumference (Wahman Manufacturing Co., Timonium, MD) were modified by the attachment of a 55 mm diameter single lobed brass cam to the axle shaft. The lobe of the cam operates two microswitches mounted 180 degrees apart (Microswitch Model BZ roller lever). Each switch, when closed, grounds a separate sensor wire. The wires pass through the wall to an adjoining room and are connected to the logic circuit as shown in Fig. 2-1. With the present equipment, up to 16 wheels can be monitored simultaneously. The logic circuit generates a signal for a given

channel (2 inputs per channel) following sequential closure of both switches. Multiple closure of either switch alone does not constitute a wheel revolution and thus generates no response. The logic circuit can be either a stand-alone device or mounted on a card installed in the internal port of a computer.

An IBM compatible 286 computer (or higher performance equivalent) was used to run the logic circuit and Data Capture Program (both obtained from AMATT Adaptive Electronics Ltd., Sherwood Park, Alberta). This program, written in "C" language, monitors the logic circuit 18 times per second, sums any detected wheel turns for each user-specified interval (1 second to 24 hours), and then writes the total number of turns in that period onto a floppy disk and on the internal hard disk with the date/time from the computer's internal clock. The data are stored in two ASCII files. The first file is written only when a batch is started or stopped, allowing for the quick inspection for problems or interference to the program. It records time and date, the state of each channel (enabled or disabled), and a 32-character description of the channel each time the Data Capture Program is started or stopped. This file has the extension ".RPT." The second file has a new line added at the user-specified sampling interval which records the date and time and the number of events (wheel turns) for each channel since the last recording to the disk. The extension for the second file is ".RAT." While the amount of data recorded is potentially very large, a single high density double-sided floppy disk (1.22 MB) will hold the

complete results from 12 channels recorded every 10 seconds for 24 hours. The cumulated total for the current day, starting at a pre-selected time, is displayed continuously on the computer monitor. This permits observation of activity in real time without disturbing the animals and also allows for a quick overview of total running for each rat on a day-to-day basis.

Both the logic circuit and the computer are powered through a non-interruptable power supply (Model BC-500, Tripp-Lite, Chicago, IL). This device provides power for approximately 30 minutes and prevents the loss of data during and following temporary power failures.

The floppy disk to which the data are being recorded can be removed between recordings to the disk and the data files copied for detailed analysis while an experiment is in progress. The data, which are stored one line for each time interval, can then be reformatted by channel and analyzed by standard statistical programs such as SPSS (SPSS, 1990). The files can be imported into PC-based spreadsheet and plotting programs, allowing for detailed analysis and direct graphing of the manipulated data and statistical values.

Subjects:

Male rats of the JCR:LA-cp strain that were lean were bred in our colony as previously described (Russell & Amy, 1986; 1989). Only phenotypically lean (+/?) animals were used. These rats are indistinguishable in any way from the parent LA/N strain.

Procedure:

They were weaned at 3 weeks of age and housed on wood chip bedding until 6 weeks of age. At this age, the rats were either placed in a previously described standardized protocol that induces prolonged running (Russell et al., 1987; 1989) or provided with food ad libitum. The rats were housed in running wheel cages in an isolated experimental room. The room lights were off from 0600 to 1800 hrs. The wheels were initially blocked to prevent rotation, and the rats left for 4 days with food and water freely available. After 4 days for acclimatization, animals were randomized to conditions, their food was removed at 1800 hrs and the wheels freed. Thereafter, the rats were weighed at 0800 hrs and fed at 1800 hrs when the lights came on. For experimental animals (N=10), the initial food allocation was 15 g/day. When running activity reached 8,000 m/day on a three-day moving average, food was increased to 18 g/day. The animals were monitored carefully, with no rat permitted to fall below 70% of initial body weight or to exceed 15,000 m/day. Freely fed rats were handled in the same manner as the food-restricted animals. Food was Wayne Rodent Blox throughout (Harlan Sprague Dawley Inc., Madison, WI). All care and treatment of the rats was in conformity with the Guidelines of the Canadian Council on Animal Care and subject to prior institutional review and approval.

RESULTS

Figure 2-2 demonstrates a typical raw data file collected by the Data Capture Program, showing hourly collection of running data from 10 rats. Six hours are shown, with each line representing one data sample. The sequential data on each line consist of time (hours, minutes, seconds, days, and date) and running data by channel.

Figures 2-3 and 2-4 show typical reformatted data recorded at 15-minute intervals, manipulated using an Excel® (1992) spreadsheet and graphed directly from the spreadsheet. The diurnal variation in the running activity of groups of 10 male rats is shown over 2 days and thus 20 observations for each point. Figure 2-3 shows the diurnal pattern of running exhibited by rats maintained on ad libitum food. They were weighed and excess new food was provided at 1800 hrs each day, as indicated by the arrow. These rats ran moderate distances (3265±1389 m/day), with multiple small bursts of activity throughout the dark period and extending 3 hours into the light period. There was no significant activity from 2100 to 0500 hrs. Figure 2-4 shows the running activity of food-restricted rats fed 18 g/day and established in a steady state. These rats ran more extensively, with a biphasic pattern of continuous running between 0600 and 1800 hrs. There was no activity over the 12-hour light period.

Figure 2-5 shows a different diurnal variation in running activity that was obtained under a different schedule of feeding and weighing the rats. In

this study, the rats were provided with ad libitum, as were the animals represented in Fig. 2-3. The only procedural difference was that the animals were weighed and new food was provided 2 hours into the light period of each daily cycle. This minimal disturbance resulted in a pattern of running resembling that of the food-restricted animals, but showed significant running during the light period as well as during the dark period. The daily total distance run was comparable to that of the rats responding to mild food restriction shown in Fig. 2-4 (5172±1844 *vs* 6551±3764 m/day for the light-disturbed and food-restricted groups, respectively. These distances are both statistically significantly greater than those run by the group shown in Fig. 2-3 ($p < 0.01$).

DISCUSSION

Computer monitoring of rat running activity as described is highly reliable and permits direct data analysis with speed and ease. In addition, details of running activity unobtainable by other recording methods are observed. The event marker technique used by other investigators (Peng & Kang, 1984; Stewart et al, 1985) reveals patterns of behavior, but is not quantitative and thus does not allow for precise statistical tests of the data. The computer-based method used by Stephan (1983) provides quantitative data on wheel turning, but provides neither data on the detailed diurnal pattern nor the ability to directly

analyze the results. The hourly collection of data shown in Fig. 2-5 clearly resulted in a loss of fine detail and illustrates the benefit of data collection over shorter time periods. Further to this, with most apparata, data are not collected without the investigator being present in the vicinity and thereby disturbing the animals. The presence of an investigator in the experimental room increases locomotor activity in rats (Teghtsoonian & Campbell, 1960). This effect is evident in Fig. 2-4. When animals were disturbed 2 hours into the light cycle, their activity levels increased dramatically.

The results reveal a complexity in the diurnal variation of running activity and a high sensitivity to changes in the treatment and handling of the animals. Current studies of the effects of drugs in our laboratory have shown significant shifts in the diurnal pattern of running that are not reflected in the sum of activity over larger blocks of time and thus would have been missed with earlier recording methods (unpublished observations). A critical factor in such experiments is the ability to leave the rats undisturbed except for daily weighing, feeding, and drug administration. The marked effect of disturbing the rats during their normal sleeping period indicates how important this is if reliable, unambiguous results are to be obtained.

The pattern of running shown in Figs. 2-3 and 2-4 is consistent with the known nocturnal character of rats and is similar to that in previous reports (Peng & Kang, 1984; Stewart et al., 1985). The pattern of running is very similar to

the diurnal variation in corticosterone activity in the rat (Akana, Cascio, Du, Levin & Dallman, 1986). Thus, in the undisturbed rat, the normal circadian rhythm of activity is also reflected in the hyperactivity of the activity anorexia syndrome. Waking the animals in the middle of the light period was clearly a highly stressful intervention, even though the handling was limited and gentle. The significant distances run in response to different manipulations of the rats suggests that the activity is a basic behavioral response to physiological stress. However, the entire diurnal pattern, including the pattern of activity during the dark period, is different under different conditions, and responses of the animals are clearly complex. Elucidation of the mechanisms controlling this activity will require very careful studies, with special attention being paid to the circadian rhythm of the rats and detailed observation of their behavior. The techniques described here would make such studies practical. The results of these should have implications for the understanding of the human activity anorexia and related disorders.

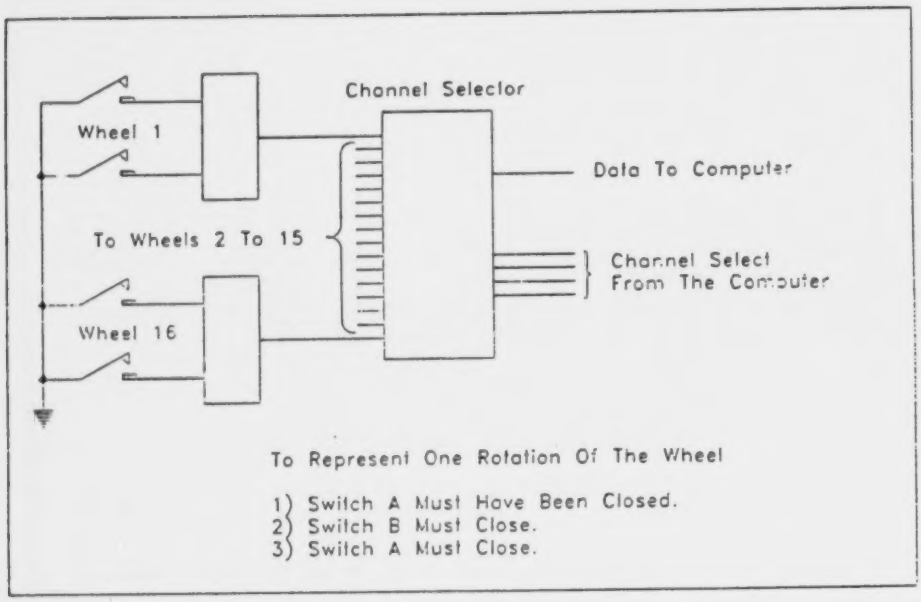
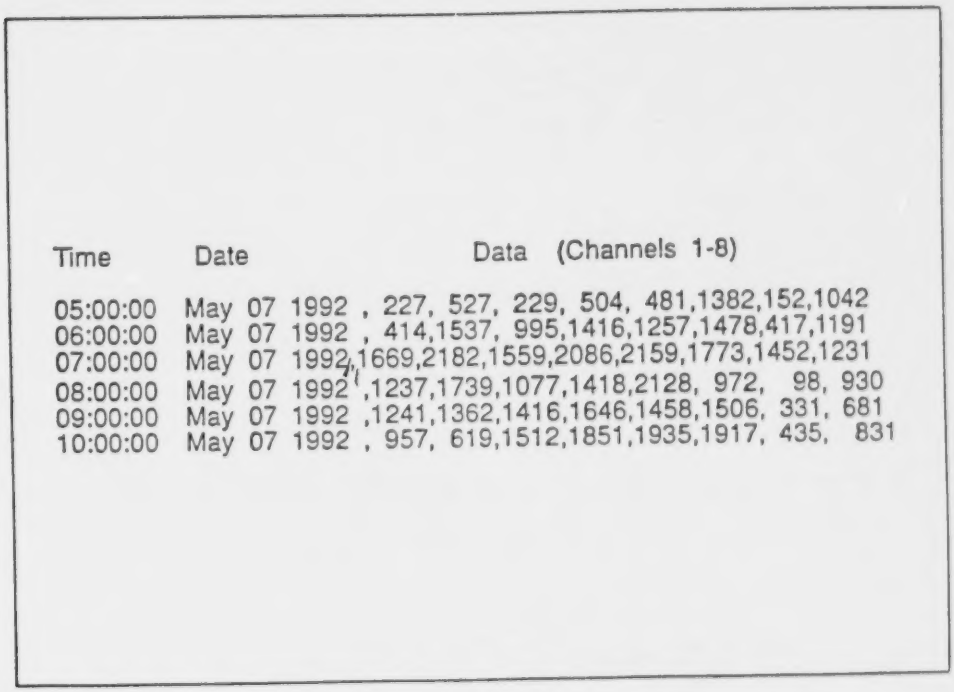


Fig. 2-1. Schematic arrangement of connections between the microswitches on the running wheels and the computer. The functions illustrated are incorporated into the logic circuit device.



```
Time        Date                    Data  (Channels 1-8)

05:00:00  May 07 1992 ,  227,  527,  229,  504,  481,1382,152,1042
06:00:00  May 07 1992 ,  414,1537,  995,1416,1257,1478,417,1191
07:00:00  May 07 1992 ,1669,2182,1559,2086,2159,1773,1452,1231
08:00:00  May 07 1992 ,1237,1739,1077,1418,2128,  972,   98,  930
09:00:00  May 07 1992 ,1241,1362,1416,1646,1458,1506,  331,  681
10:00:00  May 07 1992 ,  957,  619,1512,1851,1935,1917,  435,  831
```

Fig. 2-2. A typical raw data file collected with the Data Capture Program, showing hourly collection of running data from 8 rats.

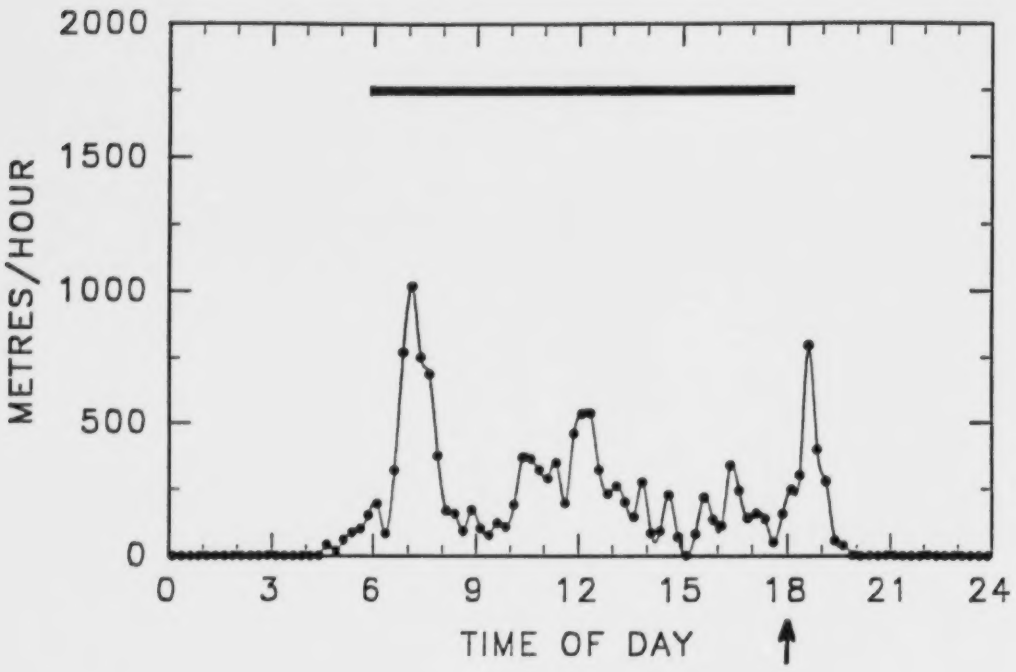


Fig. 2-3. Diurnal pattern of running in freely fed rats. The animals were weighed daily at 1800 hrs and provided with food in excess of their daily consumption. The dark horizontal line indicates the period of darkness, and the arrow, the time of feeding. The data were collected at 15-minute intervals and represent the mean activity of 10 rats over 2 days (20 observations per point). The line is a splined curve fitted to the data.

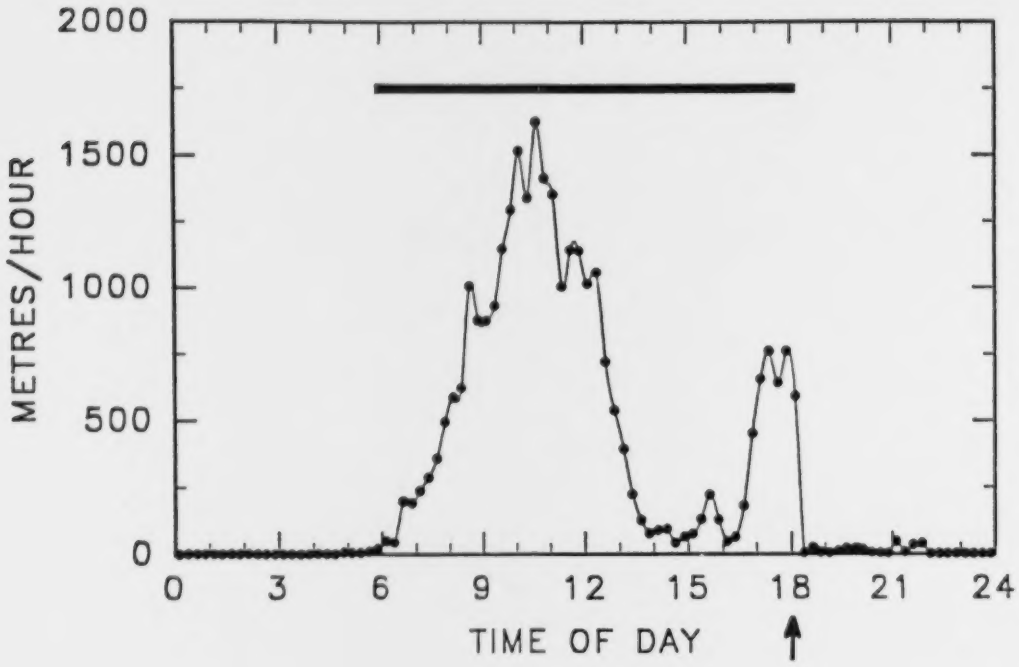


Fig. 2-4. Diurnal pattern of running in the steady state running protocol described in the text. The rats were weighed and fed 18 g of food at 1800 hrs. Other details are as in Fig. 2-2.

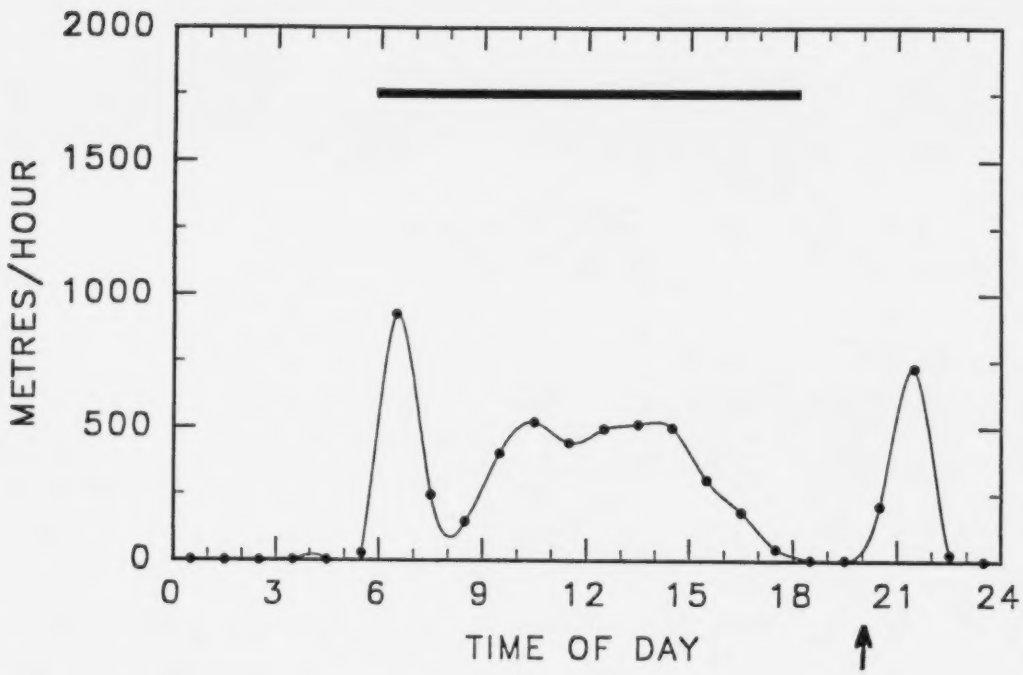


Fig. 2-5. Diurnal pattern of running in which rats were freely fed and weighed during the light cycle (2000 hrs). Data were collected hourly and represent the mean activity of 5 rats over 4 days (20 observations per point). The line is a splined curve fitted to the data.

REFERENCES

Akana, S. F., Cascio, C. S., Du, J.-Z., Levin, N., & Dallman, M. F. (1986). Reset of feedback in the adrenal cortical system. *Endocrinology* **119**: 2325-2332.

Boer, D. P., Epling, W. F., Pierce, W. D., & Russell, J. C. (1990). Suppression of food deprivation-induced high-rate wheel running in rats. *Physiology and Behavior* **48**: 339-342.

Epling, W. F., Pierce. W. D., & Stefan, L. (1983). A theory of activity-based anorexia. *International Journal of Eating Disorders* **3**: 27-46.

Epling, W. F., & Pierce, W. D. (1984). Activity-based anorexia in rats as a function of opportunity to run in an activity wheel. *Nutrition and Behavior* **2**: 37-49.

Excel,® Version 4.0 (1992). Redman, WA: Microsoft Corp.

Peng, M. T., & Kang, M. (1984). Circadian rhythm and patterns of running-wheel activity, feeding and drinking behavior of old male rats. *Physiology and Behavior* **33**: 615-620.

Russell, J. C., & Amy, R. M. (1986). Early atherosclerotic lesions in a susceptible rat model: The LA/N-corpulent rat. *Atherosclerosis* **60**: 119-129.

Russell, J. C., & Amy, R. M. (1989). Myocardial and vascular lesions in the LA/N-corpulent rat. *Canadian Journal of Physiology and Pharmacology* **64**: 1272-1280.

Russell, J. C., Amy, R. M., Manickavel, V., Dolphin, P. J., Epling, W. F., Pierce, D., & Boer, D. P. (1989). Prevention of myocardial disease in the JCR:LA-corpulent rat by running. *Journal of Applied Physiology* **66**: 1649-1655.

Russell, J. C., Epling, W. F., Pierce, W. D., Amy, R. M., & Boer, D. P. (1987). Induction of voluntary prolonged running by rats. *Journal of Applied Physiology* **63**: 2549-2553.

SPSS (1990). Reference Guide. Chicago: SPSS Inc.

Stephan, F. K. (1983). Circadian rhythms in the rat: Constant darkness, entrainment to T cycles and to skeleton photoperiods. *Physiology and Behavior* **30**: 451-462.

Stewart, K. T., Rosenwasser, A. M., & Adler, N. T. (1985). Interactions between nocturnal feeding and wheel running patterns in the rat. *Physiology and Behavior* **34**: 601-608.

Teghtsoonian, R., & Campbell, B. A. (1960). Random activity of the rat during food deprivation as a function of environmental conditions. *Journal of Comparative and Physiological Psychology* **53**(3): 242-244.

Chapter 3:

DIURNAL PATTERN OF WHEEL RUNNING ACTIVITY IN THE RAT: EFFECTS OF FOOD DEPRIVATION IN ACTIVITY ANOREXIA

INTRODUCTION

A paradoxical relationship exists between food intake and physical activity in humans: as food intake is decreased, physical activity increases. This paradoxical relationship has been recognized for many years in a condition called "anorexia nervosa" (Beumont, Abraham, & Simons, 1981; Gull, 1874; Katz, 1986). An analogous animal model for anorexia nervosa has been developed that incorporates two primary symptoms of the disorder: food restriction (dieting) and exercise (Epling, Pierce & Stefan, 1983). Food restriction that results in an increase in physical activity can be accomplished through manipulation of the size or duration of meals.

In previous studies, 24-hour totals of rat running activity were recorded using commercially available rodent running wheels fitted with mechanical or electrical turn counters. Problems that can arise with the use of these counters include: partial turns of the wheel being counted as complete turns, missed counts, and totals that need to be manually read (Boer, Epling, Pierce & Russell, 1989; Epling & Pierce, 1984; Russell, Epling, Pierce & Boer, 1987). As well, stimulation of the rats caused by direct reading of the counters in the vicinity of

these animals disturbed their behavioral patterns (Teghtsoonian & Campbell, 1960). Because of this interference, only a limited number of readings were possible and practical during any 24-hour period. Previous studies have also employed remote event recording (Peng & Kang, 1984; Stewart, Rosenwasser & Adler, 1985) or computer-based turn counting (Stephan, 1983). However, these techniques did not permit unambiguous recordings of complete wheel turns nor the precise continuous incremental collection of wheel turn data.

The purpose of this investigation was to determine the diurnal pattern of wheel running activity exhibited by rats in a 12-hour light:dark cycle when they are given free access to rodent running wheels under three different conditions: 90-minute meals, fixed meal size (15 g/day), and ad libitum food. Rats are nocturnal, being physically active at differing times throughout the dark phase, and are virtually inactive in the light phase, reflecting what may be a complex behavioral pattern. A newly developed computer-based technique (Morse, Wood, Hunt & Russell, 1993) enabled the precise continuous incremental data collection and analysis of the complex pattern of wheel running behavior exhibited by rats in these protocols.

METHODS

Equipment:

Rodent exercise cages with wheels 1.1 m in circumference (Wahman Manufacturing Co., Timonium, MD) were modified by attaching a 55 mm diameter single lobed cam to the axle shaft. The cam operates two microswitches set 180 degrees apart (Microswitch Model BZ roller lever). With this modification, an AMATT Data Collection Program (AMATT Adaptive Electronics Ltd., Sherwood Park, Alberta) enabled the continuous monitoring of 12 running wheels simultaneously (Morse et al., 1993). Both the logic circuit and the computer are powered through a non-interruptible power supply (Model BC-500, Tripp-Lite, Chicago, IL). In the case of a power failure, this device provides an alternative source of power for approximately 30 minutes, thus preventing the loss of data during and following power failures.

Wheel running data was collected in 15-minute increments throughout each protocol. The floppy disk containing the data can be removed between recording intervals and the data files copied for detailed analysis during and after the experiment. The collected data can be reformatted by channel and analyzed by standard statistical and plotting programs. The monitor display of current daily totals automatically resets each day at the pre-selected time of 0600 hrs.

Subjects:

Male lean rats of the JCR:LA-cp strain were bred as previously described (Russell & Amy, 1986; 1989). Only phenotypically lean (+/?) animals were used.

Procedure:

After weaning at 3 weeks of age, these animals were individually housed in polycarbonate cages on wood chip bedding and maintained on ad libitum food and water until the start of the experiment. Prior to and during each condition, the rats were fed pellet form chow consisting of grains and 4.5% fat (Lab Diet, PMI Feeds, Inc., St. Louis, MO).

Rats were placed in one of three experimental groups. Group 1 (ad libitum food) (n = 10) consisted of 6-week-old rats with a mean initial body weight of 227±8.51 g (data are quoted as mean and standard deviation unless otherwise described). Group 2 (food restricted to15 g/day) (n = 9) consisted of 6-week-old rats with a mean initial body weight of 147±9.35 g. Group 3 (meal restricted to 90 minutes) (n = 9) consisted of 6-week-old rats with a mean initial body weight of 199±10.76 g. Animals were randomized to treatment and each group was run independently of the others.

At 6 weeks of age, the rats were placed in an isolated environmentally controlled room where they were housed in rodent exercise cages. Room temperature was maintained at 20-22 °C, with humidity kept at 50%. The

light:dark cycle was 12:12 hours, with lights off from 0600 to 1800 hrs. All groups were weighed and fed appropriately at 1800 hrs every day for the duration of the experiments. The wheels were initially blocked to prevent rotation while the rats acclimatized for four days. After the acclimatization period, the wheels were released for all groups. The rats were not forced to run; they could choose to be sedentary, run, or exhibit any other behavioral response.

Beginning at 1800 hrs on the first day, the rats in Groups 2 and 3 were starved for 24 hours and then fed the appropriate food regime: Group 2 received 15 g of food a day and Group 3 were restricted to one 90-minute meal per day. The rats in Group 3 were given 30 g of food to consume during the 90-minute meal; any excess food was removed at 1930 hrs. Sedentary rats normally consume 22-25 g of food in a 24-hour period. Rats in Group 1 were not subjected to 24 hours of total food deprivation before the experiment. All animals were given free access to water at all times.

In the 90-minute meal protocol, at the start of the experiment the wheels were freed and the food of the rats was removed from the cages for 24 hours, beginning at 1800 hrs. After the first 24-hour period, animals were given access to 30 g of food for 90 minutes each day. The animals were allowed to consume as much food as desired during this meal period. Once the running wheel was freed, an animal had access at all times.

In the fixed food protocol, the running wheels were freed after the acclimatization period and food was removed from the cage for a 24-hour period starting at 1800 hrs. After the first 24-hour period, animals were allocated 15 g of food a day and were weighed at 1800 hrs.

In the ad libitum food protocol, after acclimatization the wheels in the animal cages were released, allowing free access. Rats were given 40 g of food a day from the start of the experiment; they were not food-deprived at any time during the experiment. At 1800 hrs excess food was removed from the cage and weighed to determine the amount consumed on that day

Data Analysis:

Linear regression analysis was done using SigmaPlot program, Version 4.0 (1989). Linear regression analysis was done on grouped data for each condition, and the slope of the regression line and associated standard error (S.E.) were calculated. Tests of statistical significance were done as described by Bailey (1976).

RESULTS

Figure 3-1 shows the time dependence of running activity under the three experimental conditions as a function of food supply and expressed as daily totals. The open circles represent the daily running activity of rats (n =

10) fed ad libitum. The slope of the linear regression line was 442±62 (S.E.) m/d/d. After Day 10, the running activity stabilized, with a mean of 3,597±1,840 m/day. The open squares represent the daily running activity of rats (n = 9) fed 15 g of food per day. The slope of the linear regression line through this data was 1,228±116 (S.E.) m/d/d. Within ten days running activity had stabilized, with a mean of 12,225±4,090 m/day. The closed circles represent the daily running of rats (n = 9) restricted to one 90-minute period access to food. The slope of the linear regression line was 1,928±287.7 m/d/d. The rats' physical condition deteriorated rapidly; body weight loss exceeded 20% in this protocol, requiring the termination of this experiment after four days. The slopes of the linear regression lines from each group differed significantly ($p > 0.001$ Group 2 *vs* Group 1; $p > 0.02$ Group 3 *vs* Group 2). All regression lines intersected at 1000 m/day at Day -1, demonstrating that there was no significant difference between groups at the start of each condition.

Figure 3-2 shows the average body weight of the rats in grams. The open circles represent the body weight of rats fed ad libitum. The open squares represent the body weight of rats fed 15 g of food per day, and the closed squares, the body weight of rats restricted to one 90-minute meal. The rats restricted to one 90-minute meal did not adapt to the dietary regime, resulting in a dramatic weight loss, while the other groups maintained or even increased their body weight. Figure 3-3 shows the food consumed over the first ten days

of the experiment. The closed circles represent the food consumed by rats fed ad libitum and the closed squares, the food consumed by rats restricted to one 90-minute meal. Rats allocated 15 g of food per day consumed the entire amount given. Rats restricted to one 90-minute meal began to self-restrict by Day 4, while further increasing wheel running activity.

Figure 3-4 shows the diurnal pattern on Day 4 by rats fed ad libitum, with data recorded at 15-minute intervals. Each dot represents 10 observations. Since rats are nocturnal, their wheel running activity was confined to the dark phase and the early part of the light period. Running activity was thus less intense, occurring in discreet intervals throughout the course of the experiment. No wheel running activity occurred during the later six hours of the light phase.

Figure 3-5 represents the diurnal variation in wheel running on Day 4 by rats restricted to 15 g of food per day. Wheel running activity was basically confined to the dark phase. The running pattern was triphasic for the first week, with significant troughs of decreased activity occurring between each peak. Running activity began just before the dark phase and ended with a peak of anticipatory activity just before feeding at the end of the dark phase. A biphasic pattern developed during the later days of the study, as previously reported (Morse et al., 1993). Rats left in this protocol will eventually become emaciated, running as much as 26,000 m/day. Their diurnal pattern of activity eventually collapses, resulting in continuous wheel running throughout the dark

phase and in most of the light phase. In contrast, Fig. 3-6 shows the start of the breakdown of the diurnal variation in running of rats in the unstable protocol (90-minute meal) as early as Day 1. These rats were virtually running continuously by the fourth day of the experiment. Figure 3-7 shows the diurnal variation during Day 4. No period of zero activity occurred, a behavior which is highly abnormal. Figure 3-7 shows the increase in running activity and the breakdown of the normal diurnal pattern of activity throughout the four days prior to the termination of the experiment.

DISCUSSION

Anorectic behavior in humans is characterized by a loss of appetite, decreased body weight, hyperactivity, and endocrine abnormalities which result in amenorrhea in females and low sex drive in males (Casper, Schoeller, Kushner, Hnilicka & Trainer-Gold, 1991; Gold & Halmi, 1989; Kron, Katz, Gregory & Weiner, 1978). Evidence suggests that these symptoms are the product of chaotic dieting. A paradoxical relationship exists between food restriction and physical activity in human anorectic behavior: decreased food intake results in an increase in physical activity. Locomotor activity returns to control levels when food intake and body weight normalize (Casper et al., 1991).

Anorectic behavior is also seen in food-deprived rats that are given free access to a rodent running wheel. Young rats subjected to Epling and Pierce's

classic activity anorexia paradigm lost weight and exhibited excessive locomotor activity. Food-deprived female rats became anestrus (Watanabe, Hara, & Ogawa, 1992), while serum levels of testosterone were reduced as much as 80% in food-deprived males (Bergendahl, Perheentupa, & Huhtaniemi, 1989). Overall, the animal model of activity anorexia has functional similarity to the human condition, making it a useful model for the investigation of the determinants of anorexia under controlled conditions (Epling & Pierce, 1991).

Wheel running activity in rats is a function of food supply. The amount of food and the way it is allocated have a marked effect on running behavior. When 6-week-old male rats were given free food and continual access to rodent running wheels, their food consumption increased modestly to 25-30 g/day, as compared to the 22-25 g/day consumed by sedentary animals. These animals increased their activity to a moderate level of 3,600 m/day for the duration of the study. They adapted well, eating increased amounts of food in response to the greater activity and energy output, and had an appropriate body weight gain. In comparison, 6-week-old male rats restricted to 15 g/day increased their running activity dramatically day by day to 14,000 m/day by the tenth day. Some animals ran in excess of 26,000 m/day, while the mean for all animals in this group was 12,225 m/day for the duration of the study. If allowed to continue indefinitely, these rats would self-restrict food intake and lose body weight (Russell et al., 1987).

When access to food rather than the amount of food given is restricted, the onset of activity anorexia is exacerbated. Rats restricted to one 90-minute meal self-restrict food intake within two days of the start of the study, while sharply increasing wheel running activity. In this protocol rats physically decompensate rapidly, losing in excess of 20% of their starting body weight within four days. In contrast, rats restricted to one 90-minute meal, but not allowed access to a running wheel, will regain any initial weight loss and will adapt and survive, consuming 10 to 12 g/day.

The body weight of rats restricted to 15 g/day remained relatively constant throughout a 21-day study. In comparison, body weight decreased rapidly when rats were restricted to one 90-minute meal. The fact that animals restricted to 15 g/day ran excessively while maintaining a relatively consistent body weight suggests that food manipulation rather than body weight may be the main impetus for hyperactivity in activity anorexia. Epling and Pierce (1988) suggest that this increased running activity in response to decreased availability of food is a behavior that has survival value in that it initiates food seeking behavior.

Rats on different feeding schedules exhibit marked variation in the pattern of wheel running. Qualitative studies of the diurnal patterns of wheel running have demonstrated the complexity of this behavior (Coleman, Harper, Clarke & Armstrong, 1982). This complexity has led us to examine and

measure, in precise increments of time, the quantitative terms of running activity exhibited by rats on free food, restricted food size, and restricted meal schedules.

The rats increasingly ran throughout the dark and the major part of the light phase—behavior which was highly abnormal. By the end of the fourth day, there was a complete breakdown of the diurnal pattern of activity. In contrast, rats fed ad libitum or 15 g/day ran primarily during the dark phase (Figs. 3-4 and 3-5). Since rats are nocturnal and therefore normally active in the dark phase, this suggests that moderate food restriction results in changes in the physiological systems that modulate rest and activity cycles. The possible importance of the breakdown in the diurnal pattern of activity exhibited by moderately food-restricted animals should not be dismissed.

Many physiological systems have been implicated in the control of food intake and metabolism, including the endogenous opioid system. Recent studies of food intake behavior in humans suggest that the endogenous opioids may modulate food intake (de Zwaan & Mitchell, 1992; Leibowitz, 1992; Tepper, Weizman, Apter, Tyano & Beyth, 1992). Endogenous opioids have also been found to play a role in the feeding behavior of rats. In these animals, as endogenous opioid levels increase, food intake decreases (Davidson, McKenzie, Tujo & Bish, 1992). Davidson and associates (1992) demonstrated that food deprivation alone will produce an analgesic effect in the rat by stimulating the endogenous opioid system. Other studies have shown that food-deprived rats

will exercise excessively if given free access to a rodent running wheel (Epling et al., 1983; Routtenberg & Kuznesof, 1967; Russell et al., 1987). Physical exercise also stimulates the endogenous opioid system. The combined effects of food deprivation and excessive physical activity on the endogenous opioid system may maintain anorectic behavior in rats (Boer, Epling & Pierce, 1989).

Activity anorexia may best be described as an addiction resulting from chronic hyperstimulation of the endogenous opioid system. Endogenous opioids released as a consequence of dieting and exercise may reinforce and perpetuate self-starvation. Tolerance resulting from chronic stimulation of the opioid system may be countered by a further reduction in food intake and a concomitant increase in locomotor activity. This paradoxical relationship between food intake and exercise culminates in a self-destructive condition. The ability to manipulate and precisely measure the resultant diurnal pattern of wheel running activity exhibited by food-deprived rats offers the possibility of elucidating the physiological mechanisms underlying activity anorexia.

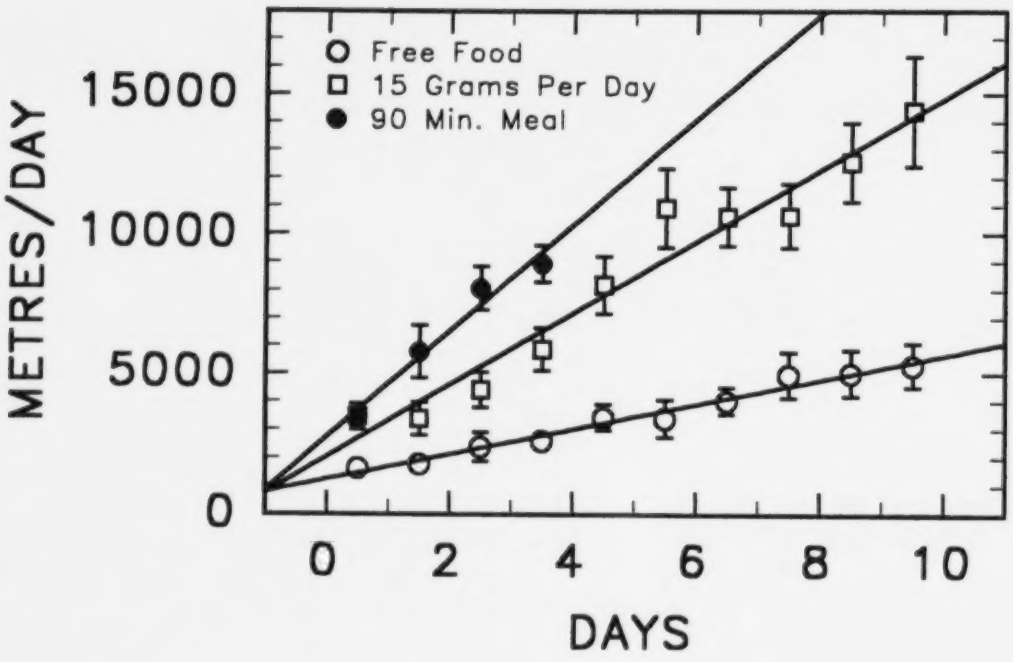


Fig. 3-1. Average wheel running activity as a function of food supply in free food (n = 10), 15 g/day (n = 9), and 90-minute conditions (n = 9).

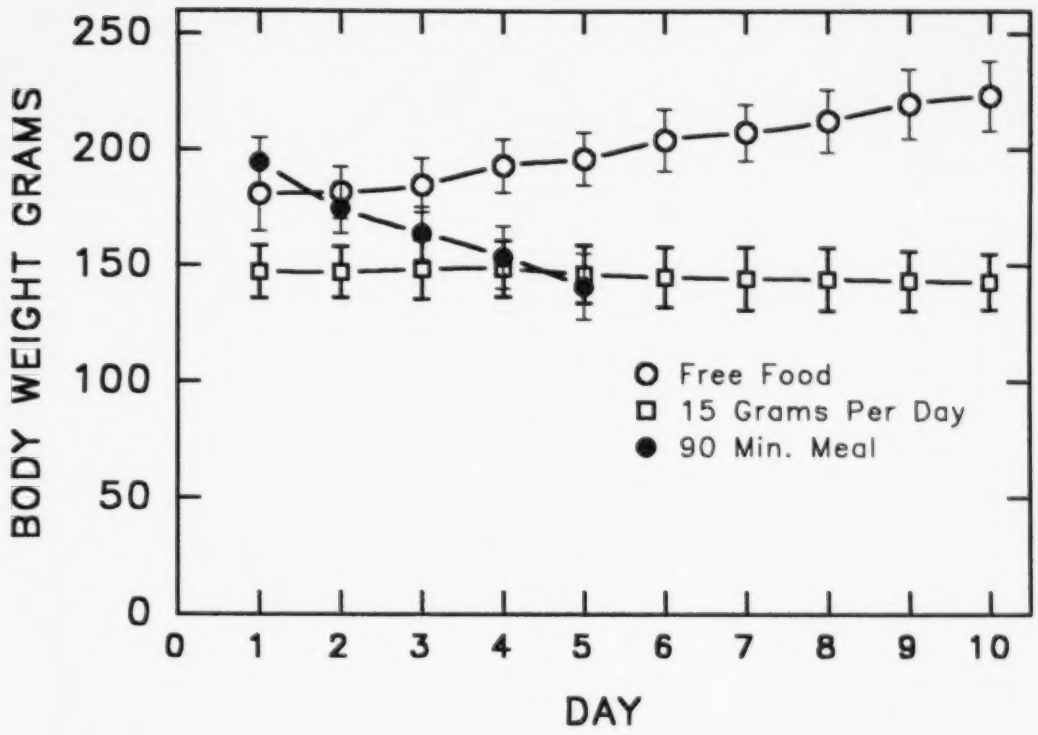


Fig. 3-2. Average body weight of all rats in free food (n = 10), 15 g/day (n = 9), and 90-minute conditions (n = 9).

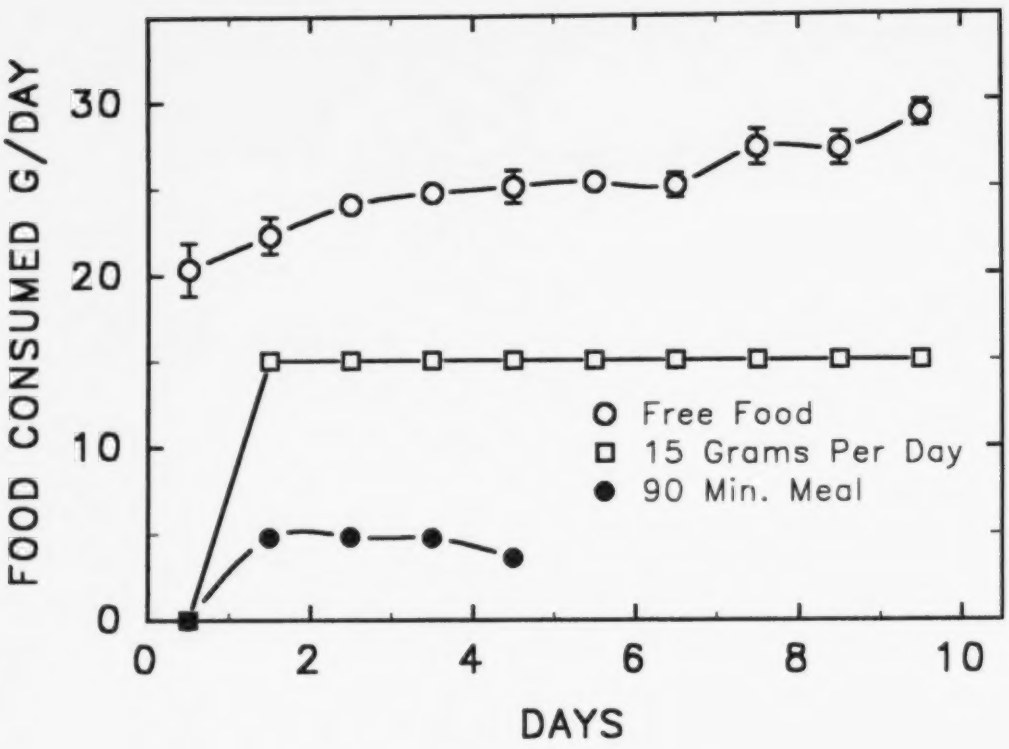


Fig. 3-3. Average food consumed by all rats in free food, 15 g/day, and 90-minute conditions.

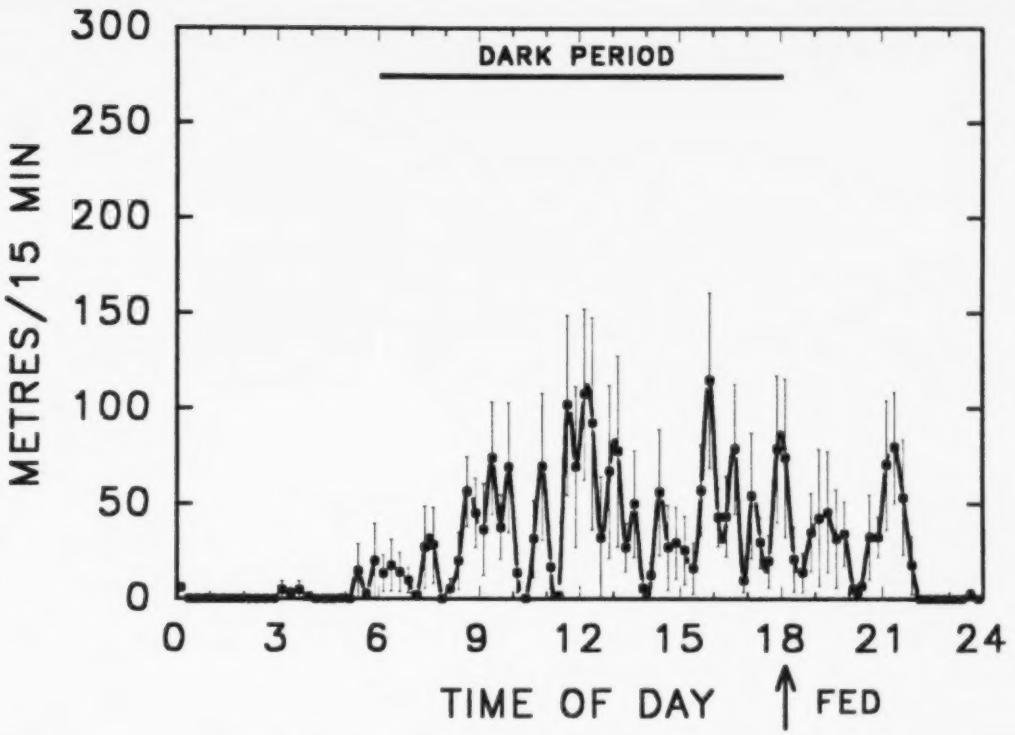


Fig. 3-4. Diurnal variation in wheel running under free food condition, Day 4. Data represent the mean running of 10 rats in 15-minute intervals. Vertical bars indicate standard error of the mean. The arrow indicates time of day at which the rats were fed.

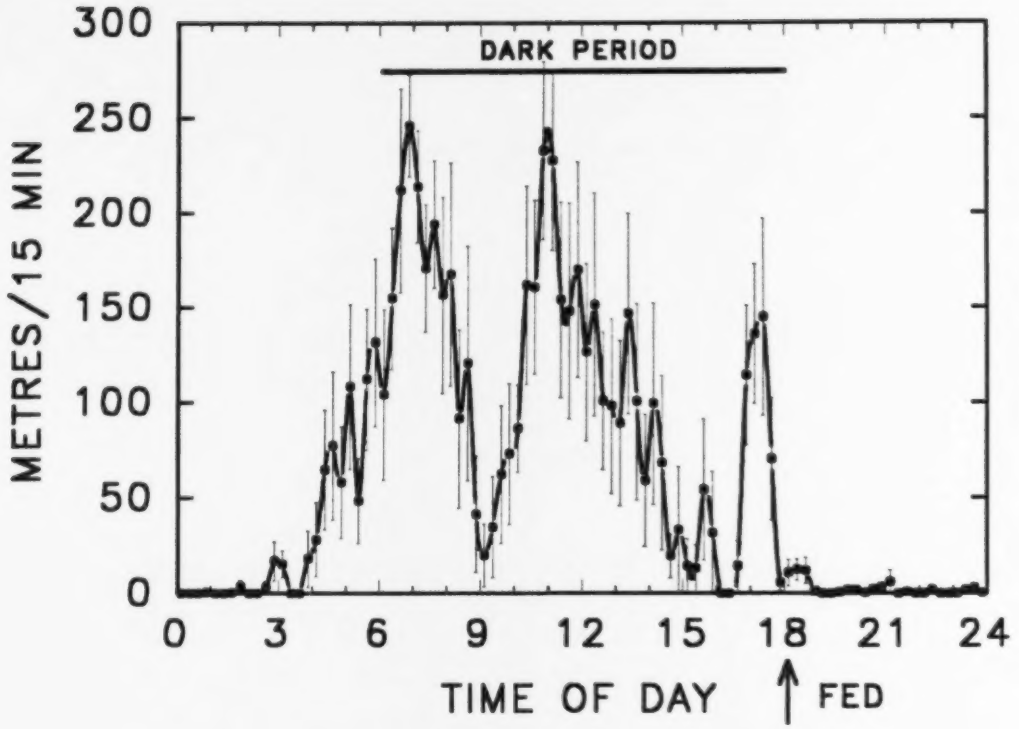


Fig. 3-5. Diurnal variation in wheel running under restricted food (15 g/day), Day 4. Data represent the mean running of 9 rats in 15-minute intervals. Vertical bars indicate standard error of the mean. The arrow indicates time of day at which the rats were fed.

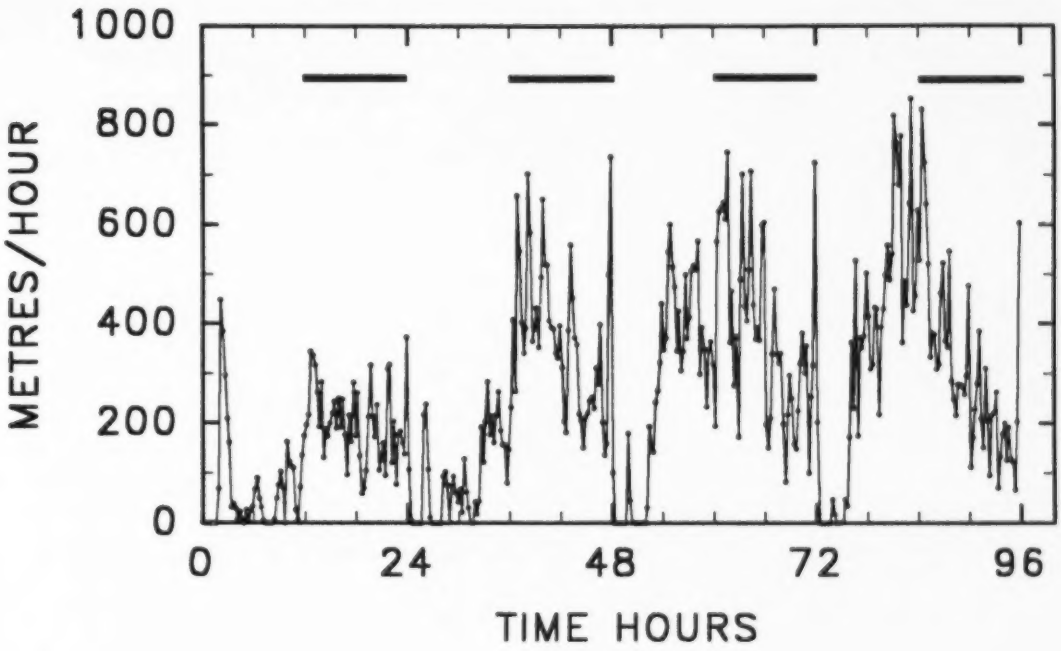


Fig. 3-6. Diurnal variation in wheel running for the first 96 hours under the 90-minute condition. Data represent the mean running of 9 rats in 15-minute intervals. The arrow indicates time of day at which the rats were fed.

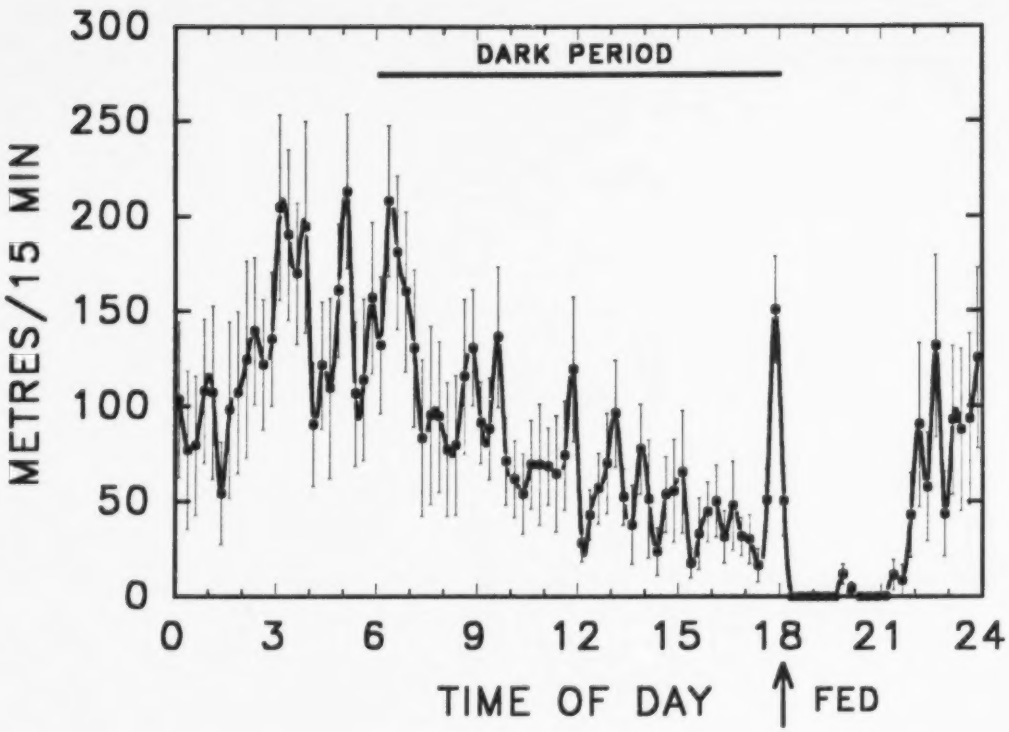


Fig. 3-7. Diurnal variation in wheel running under the 90-minute meal condition, Day 4. Data represent the mean running of 9 rats in 15-minute intervals. Vertical bars indicate standard error of the mean.

References

Bailey, N. T. J., (1976). *Statistical Methods in Biology.* London: Hodder and Stoughton.

Bergendahl, M., Perheentupa, A., & Hubtaniemi, I. (1989). Effects of short term starvation on reproductive hormone gene expression, secretion and receptor levels in male rats. *Journal of Endocrinology* **121**: 490-417.

Beumont, P. J. V., Abraham, S. F., & Simons, K. G. (1981). The psychosexual histories of adolesent girls and young women with anorexia nervosa. *Psychiatric Medicine* **11**: 131-140.

Boer, D. P. (1989). *Determinants of Excessive Running in Activity Anorexia.* Unpublished doctoral dissertation, University of Alberta, Alberta.

Boer, D. P., Epling, W. F., Pierce, W. D., & Russell, J. C. (1990). Suppression of food deprivation-induced high-rate wheel running in rats. *Physiology and Behavior* **48**: 339-342.

Casper, R. C., Schoeller, D. A., Kushner, R., Hnilicka, J., & Trainer-Gold, S. T. (1991). Total daily energy expenditure and activity level in anorexia nervosa. *American Journal of Clinical Nutrition* **53**: 1143-1150.

Coleman, G. J., Harper, S., Clarke, J. D., & Armstrong, S. (1982). Evidence for a separate meal-associated oscillator in the rat. *Physiology and Behavior* **29**: 107-115.

Davidson, T. L., McKenzie, B. R., Tujo, C. J., & Bish, C. K. (1992). Development of tolerance to endogenous opiates activated by 24-hr food deprivation. *Appetite* **19**: 1-13.

de Zwaan, M., & Mitchell, J. E. (1992). Opiate antagonists and eating behavior in humans: A review. *Journal of Clinical Pharmacology* **32**: 1060-1072.

Epling, W. F., & Pierce, W. D. (1984). Activity-based anorexia in rats as a function of opportunity to run in an activity wheel. *Nutrition and Behavior* **2**: 37-49.

Epling, W. F., & Pierce, W. D. (1988). Activity-based anorexia: A biobehavioral perspective. *International Journal of Eating Disorders* **7**: 475-485.

Epling, W. F., & Pierce, W. D. (1991). *Solving the Anorexia Puzzle: A Scientific Approach.* Toronto: Hagrefe and Haber.

Epling, W. F., Pierce, W. D., & Stefan, L. (1983). A theory of activity-based anorexia. *International Journal of Eating Disorders* **3**: 27-46.

Gold, P. W., & Halmi, K. A. (1989). Affective and eating disorders: Appetite, weight regulation, and neuroendocrine function. *Psychopharmacology Bulletin* **25**(3): 433-438.

Gull, W. (1874). Anorexia nervosa (apepsia) hysteria, anorexia hysteria. *Transcripts of the Clinical Society, London* **7**: 22-31.

Katz, J. L. (1986). Long-distance running, anorexia nervosa, and bulimia. *Comprehensive Psychiatry* **27**(1): 74-78.

Kron, L., Katz, J. L., Gozynski, G., & Weiner, H. (1978). Hyperactivity in anorexia nervosa: A fundamental clinical feature. *Comprehensive Psychiatry* **19**(5): 433-440.

Leibowitz, S. F. (1992). Neurochemical-neuroendocrine systems in the brain controlling macronutrient intake and metabolism. *Trends in Neuroscience* **15**(12): 491-497.

Morse, A. D., Hunt, T., Wood, G. O., & Russell, J. C. (1993). Measurement of diurnal variation of running activity in the rat. *Physiology and Behavior*, submitted for publication.

Peng, M. T., & Kang, M. (1984). Circadian rhythms and patterns of running-wheel activity, feeding and drinking behaviors of old male rats. *Physiology and Behavior* **33**: 615-620.

Routtenberg, A., & Kuznesof, A. W. (1967). Self-starvation in rats living in activity wheels on a restricted feeding schedule. *Journal of Comparative and Physiological Psychology* **64**(3): 414-421.

Russell, J. C., & Amy, R. M. (1986). Early atherosclerotic lesions in a susceptible rat model: The LA/N-corpulent rat. *Atherosclerosis* **60**: 119-129.

Russell, J. C., & Amy, R. M. (1989). Myocardial and vascular lesions in the LA/N-corpulent rat. *Canadian Journal of Physiology and Pharmacology* **64**: 1272-1280.

Russell, J. C., Epling, W. F., Pierce, W. D., Amy, R. M., & Boer, D. P. (1987). Induction of voluntary prolonged running by rats. *Journal of Applied Physiology* **63**: 2549-2553.

SigmaPlot Scientific Graphing Software, Version 4.0 (1989). Corte Madera, CA: Jandel Scientific.

Stephan, F. K. (1983). Circadian rhythms in the rat: Constant darkness, entrainment to T cycles and to skeleton photoperiods. *Physiology and Behavior* **30**:451-462.

Stewart, K. T., Rosenwasser, A. M., & Adler, N. T. (1985). Interactions between nocturnal feeding and wheel running patterns in the rat. *Physiology and Behavior* **34**:601-608.

Teghtsoonian, R., & Campbell, B. A. (1960). Random activity of the rat during food deprivation as a function of environmental conditions. *Journal of Comparative and Physiological Psychology* **53**(3):242-244.

Tepper, R., Weizman, A., Apter, A., Tyano, S., & Beyth, Y. (1992). Elevated plasma immunoreactive beta endorphin in anorexia nervosa. *Clinical Neuropharmacology* **15**(5): 387-391.

Watanabe, K., Hara, C., & Ogawa, N. (1992). Feeding conditions and estrous cycle of female rats under the activity-stress procedure from aspects of anorexia nervosa. *Physiology and Behavior* **51**: 827-832.

Chapter 4:

GENERAL DISCUSSION

INTRODUCTION

In modern societies, 30% of the population is affected by disorders of body weight and metabolism (Leibowitz, 1992). These disorders include obesity, bulimia nervosa, and anorexia nervosa. Dieting and food obsessions are primary characteristics of these eating disorders.

An eating disorder commonly referred to as "anorexia nervosa" is characterized by dieting and hyperactivity (Epling & Pierce, 1991; Katz, 1986). The estimated incidence for anorexia nervosa in otherwise healthy adolescents and young adults is estimated to be as high as 3%, and the mortality for diagnosed patients is between 5% and 21% (Yates, 1990). Long-term morbidity and recurrences are common.

HISTORY

Anorexia nervosa is not just a syndrome of the 20th century; cases have been reported throughout recorded history. As early as the 4th century, St. Jerome was instructing his female protegées to be pale and thin with fasting. Blessila, a student of St. Jerome, died of this anorectic regimen (Lacey, 1982). She may be the first recorded victim of self-starvation.

Anorectic behavior among males and females was first clinically described by Morton in a textbook of medicine published in 1694. In this textbook, *Phthisiologica: Or a Treatise of Consumptions,* Morton gives the first medical account of anorectic behavior, a condition he referred to as "nervous consumption." Morton vividly defined this condition as being "wasted with the greatest degree of a consumption (like a skeleton only clad with skin)" (Morton 1694:9). In describing the patients' condition, he also noted that there was no fever, only that their appetite was diminished and their digestion irregular (Bruch, 1973). According to Morton, the etiology of nervous consumption can be traced to disturbances of the psyche, from feelings of "sadness and anxious cares" (Bliss & Branch, 1960:10).

Two centuries later, Gull detailed another account of self-starvation, which he initially referred to as "apepsia hysterica." However, by 1873 Gull had adopted a more descriptive term for this disorder: "anorexia nervosa" (Dally, 1967). This term better described what Gull considered as being primary in the etiology of the disorder: "The want of appetite (anorexia) was due to a morbid state of mind" (nervosa) (Gull, 1874:23). Like the mentalists of today, Gull considered anorexia nervosa a mental illness. According to Gull, the clinical characteristics of anorexia nervosa "were those of starvation only, without any signs of visceral disease. Such patients, though extremely wasted, complain of no pain, nor indeed of any malaise..." (Gull, 1874:22). Further to this

description, he stated that anorexia nervosa was marked by hyperactivity, constipation, and, in females, amenorrhea. All of these symptoms he saw as occurring in the absence of any physical illness (Epling & Pierce, 1991).

While Gull was investigating and describing the symptoms of anorexia nervosa, an independent report was published by Lasèque in which he referred to the disorder as "anorexia hysterica" (Lasèque, 1873). In 1873, Lasèque stated that this disorder was dependent on a psychic disturbance and a distorted body image (Epling & Pierce, 1991). Later, Lasèque questioned the use of the name "anorexia" because it emphasized the phenomenological aspects of the disorder, not scientific knowledge (Thoma, 1967). Lasèque thought of anorexia nervosa as a form of hysteria, and "he saw hysteria as a predominantly hereditary disturbance of the central nervous system" (Thoma, 1967:10). However, in an essay entitled "L'anorexia hystérique," he emphasized that the etiology of anorexia hysteria was emotional, involving disturbed relationships (Bliss & Branch, 1960).

Modern Perspectives on Activity Anorexia

The influence of Morton's, Gull's, and Lasèque's descriptions of the symptomatology of anorexia nervosa is evident in modern theories, which reflect their operational criteria for diagnosing anorexia nervosa. These criteria emphasize, to varying degrees, the behavior, psychopathology, and abnormal

endocrine function. Russell has suggested the following three criteria for diagnosing this syndrome: "1) behavior that is designed to produce marked weight loss; 2) the characteristic psychology of morbid fear of becoming fat; and 3) evidence of an endocrine disorder—in females, amenorrhea, and in males, loss of sexual potency and interest" (Russell 1970:134). Other diagnostic criteria have been suggested; however, they generally reflect Russell's three-point criteria.

Medical Perspective:

According to the *Diagnostic and Statistical Manual of the American Psychiatric Association* (DSM-III-R) (1987), anorexia nervosa is an eating disorder characterized by: self-starvation, distorted body image, fear of gaining weight or becoming fat, and amenorrhea in females or a lower sex drive in males. From this perspective, anorexia nervosa is a mental illness. In the mental illness view, anorexia nervosa is described as a subconscious disturbance or as a neurosis by psychoanalytical theory. Thomas Szasz concludes: "Our adversaries are not demons, witches, fate or mental illness. We have no enemy whom we can fight, exorcise, or dispel by 'cure.' What we do have are problems in living—whether these be biologic, economic, political, or sociopsychological" (Epling & Pierce, 1991:22). Proponents of the medical model argue that mental illness is a myth, therefore "anorexia nervosa as a type

of mental illness is also a myth" (Epling & Pierce, 1991:22). The medical model explains any illness as a product of physical disease (i.e., a pathophysiological process). Anorexia nervosa is therefore not a product of distorted thought processes; rather, it stems from overt behaviors such as dieting, excessive physical activity, and neurological changes that result in physiologically determined anorexic behavior (Epling & Pierce, 1991).

Psychodynamic Perspective:

From the psychoanalytic perspective, anorexia nervosa originates from psychosexual difficulties. For females, "factors such as fantasies of oral impregnation, sexual immaturity, rejection of femininity, [and] fear of pregnancy" (Blaney, 1985:334) are proposed as contributing to the etiology of the syndrome. The fear of maturing and the exigencies of puberty result in the defence mechanism, anorexia nervosa (Crisp, 1980). From this perspective, anorectic behavior results from distorted thought processes and personality and is viewed as an emotional disease. However, there is emerging evidence that suggests anorexia nervosa is a somatic disorder.

There is growing evidence that distorted thought processes <u>follow</u> rather than precede anorectic behavior. Katz (1986) reported that restricted food intake, weight loss, and excessive physical activity precede food preoccupation and distorted thought processes. Further studies indicate that depression, body

image distortion, and endocrine dysfunction follow self-starvation and excessive physical activity (Beumont, Booth, Abraham, Griffiths & Turner, 1983; Keys, Borzek, Henschel, Mickelson & Taylor, 1950).

There is physiological evidence supporting the pathological sequence of events described by Katz (1986). Cognitive dysfunction may be mediated by starvation-induced neuroendocrine changes specifically related to glucocorticoid levels. Cognitive impairment has been attributed to increased plasma levels of endogenous cortisol in anorexia nervosa patients (Laessle, Fischer, Fichter, Pirke & Krieg, 1992). Increased plasma cortisol levels are an adaptation by the organism to either intermittent or chronic food restriction (Fichter & Pirke, 1990). Abnormalities in this endocrine system occur on a continuum, the severity of these reflecting the degree of food deprivation and weight loss (Laessle et al., 1992). Glucocorticoids may therefore play a role in modulating central nervous system functions involved in the perception and processing of information (Henkin, 1975).

Anorexia nervosa is often considered a syndrome affecting primarily adolescent women, yet both sexes can be affected. The psychoanalytical perspective provides an explanation for anorectic behavior in females, but fails to account for this behavior in males. The prevalence rate for anorexia nervosa in males is 22.5 per 100,000 population (Lucas, Beard, O'Fallon & Kurland, 1991). Further, investigators have found no common pattern in the

psychosexual history of anorectics, which suggests that sexual factors are not of etiological origin in anorectic behavior (Beumont, Abraham & Simson, 1981; Dally, Gomez & Isaacs, 1979). In addition, anorectic behavior can occur in individuals with genetic disorders such as Turner's Syndrome, where secondary sexual features do not develop (Kron, Katz, Gozynski & Weiner, 1978).

In summary, anorexia nervosa is viewed as an emotional disorder. Concepts such as a loathing of self (Janet, 1903), a morbid mental state (Gull, 1874), a pubertal form of melancholia (Freud, 1954), and a defective sense of self (Strober, 1991) have all emphasized the psychic state as being primary in the etiology of this disorder. However, evidence supports the concept that anorectic behavior is a response to a physiological stressor such as chaotic dieting and excessive physical exercise that, if sufficiently severe, initiates neurochemical and neurohormonal changes that result in cachexia and the distortion of thought processes. Anorexia nervosa should therefore be considered a somatic disease and not a psychic disorder.

Familial Perspective:

Rather than psychosexual difficulties, the familial approach implicates an "enmeshed family pattern" (Minuchin, Rosman & Baker, 1978) as leading to anorectic behavior in adolescent children. The enmeshed family pattern can be defined as family members having a smothering and controlling interest in each

other's affairs coupled with pathological concern for each other's well-being. From this perspective, anorectic behavior is a response to dysfunctional family dynamics. The dysfunctional interaction within the family perpetuates the child's anorectic behavior and in turn maintains the enmeshed family pattern (Epling & Pierce, 1988). When the adolescent child seeks normal autonomy within this dysfunctional family pattern, it is perceived as a threat to family harmony and togetherness. As the family seeks to re-establish the facade of harmony and togetherness, the child is forced to adopted a "sick role"—that of anorexia. The child's sickness now becomes the rallying cause for family unity. The family only wants to protect the child (Minuchin et al., 1978).

From the familial perspective, expressed emotions such as critical comments are an indicator of unresolved family conflict. The child, wanting to avoid family conflict, adopts the sick role. As a result, the anorectic behavior of the child serves to meet the pathological needs of the family.

The familial approach excludes objective factors such as physical activity and neurological changes exhibited in anorectic behavior. The focus of family theory is on subjective feelings of fear and control. As stated previously, these feelings and fears (mental states) of the anorectic patient are by-products of chaotic dieting, weight loss, and excessive physical exercise. These behavioral and physiological responses result in neurochemical and

neuroendocrine abnormalities that lead to cachexia and distorted thought processes (Laessle et al., 1992; Leibowitz, 1992; Morley & Blundell, 1988).

The familial perspective emphasizes the effects of emotional entanglement in providing a motive for anorectic behavior. Motive for this disorder is better understood as the effects of verbal and neurochemical reinforcement rather than by inner psychological states. The impetus for anorectic behavior is not psychological states; rather, chaotic dieting and excessive physical exercise that are reinforced by sociocultural standards may be responsible for initiating and maintaining anorectic behavior. Epling and Pierce (1988) state that two primary characteristics of anorexia nervosa, chaotic dieting and exercise, are conveyed to the child through family interaction. Thinness and physical fitness are reinforced by the family and society, encouraging the child to exhibit anorectic behavior. What family therapy does is change the setting and alter the contingencies of reinforcement that prompt the child to exhibit anorexia.

Sociocultural Perspective:

Members of society that meet a beauty standard are rewarded with social acceptance and economic security. Thinness, as a beauty standard, has been emphasized in modern western culture for many years. The sociocultural perspective focuses on society's preoccupation with thinness as

being pivotal in the development of anorectic behavior. Thinness is rewarded with popularity, and the constant need for acceptance and approval is the impetus for anorectics to develop and maintain their thinness (Branch & Zurman, 1980; Garner & Garfinkel, 1980).

Throughout history, society has often overvalued the qualities of thinness. Written accounts of this are found as far back as the 4th century when women were instructed by religious leaders to be thin and pale with fasting (Lacey, 1982). For women, thinness was a gauge of godliness. The more emaciated the woman, the more godly and desirable she became. Thinness resulted in status and popularity much the same way it does today.

The value of thinness has placed demands on women as well as on men. These demands have served to prompt abusive and severe changes to body shape and size. Through compulsive exercise and dieting, men and women of the 20th century earnestly seek what has not been endowed by nature. Society' beauty standards reinforce anorectic behavior in both sexes, implicating a role for sociocultural demands in initiating this disorder. Females appear to be most vulnerable to social demands of beauty; this may account for the variance in prevalence rates between males and females diagnosed with this disorder.

Behavioral Perspective:

The clinical label for self-starvation—anorexia nervosa—emphasizes a common opinion that inner mental states are the impetus for this behavior. This concept is evident when one analyzes the literal meaning of the term. "Anorexia" means loss of appetite, and "nervosa" means a morbid state of mind (Gull, 1873). Together, the two terms define anorexia nervosa as the loss of appetite due to a morbid state of mind. This morbid state of mind includes distorted thought processes and personality disorders. Using this definition, anorectic behavior is considered a neurotic disorder (Epling & Pierce, 1988).

Although many investigators and clinicians find this mental explanation acceptable, "a genuinely scientific account of starvation can not rely on inferred and subjective processes" (Epling & Pierce, 1988:17). Behaviorists consequently argue that science cannot be based on subjective beliefs, perceptions, or thoughts and feelings. These cognitive processes are viewed by behaviorists as byproducts of environmental experiences and are the direct result of objective activity (Skinner, 1976). In this regard, self-starvation is considered a normal response to abnormal environmental conditions. From this perspective, overt behavior is what should be studied to determine the cause of the disorder and what conditions maintain the behavior. Once these are determined, possible interventions can then be evaluated.

Behavioral theory emphasizes overt behavior; therefore, the etiology of anorectic behavior is a function of learned food deprivation maintained by contingencies of reinforcement (Blindor, Freeman & Steinkard, 1970). Environmental conditions and physiological systems are involved in the reinforcement of behavior (Skinner, 1976). Anorectic behavior (and for that matter, any other behavior) involves the peripheral and central physiological systems. Behavior changes these systems, and these systems in turn mediate behavior (Skinner, 1976). In order to understand and change anorectic behavior, the primary foci for the behaviorist are eating behavior and body weight (Epling & Pierce, 1988).

For the behaviorist, weight gain and changing eating behavior are priorities in treating severe self-starvation. Modifying poor eating patterns and subsequent low body weight in severely affected individuals most often involves hospitalization where they can be confined to bed and where items that are not essential, such as television and reading materials, can be removed from the patient's room. The goal is for the anorectic to gain weight and eventually to achieve and maintain a normal body weight. In order to achieve this goal, both positive and negative reinforcement are used. This technique can also be used with patients with less severe anorexia in a less restricted environment such as the home.

Following initial weight gain, the patient is positively reinforced by having privileges that were initially withheld reinstated. These privileges may include reading, watching television, and socializing with friends. Negative reinforcement "occurs when the anorectic increases eating and weight in order to get out of bed, go out of the room" (Epling & Pierce, 1988:101), and get off the program. In addition, behaviorists may implement systematic desensitization, behavioral contracts, and family counselling in order to assist and maintain normal functioning patterns for the patient (Halmi, 1985).

Epling and Pierce (1988) studied treatments that incorporated some forms of behavioral technique were most effective in eliminating anorectic behavior. They determined that, out of 78 patients receiving behavioral therapy, all but one benefited from this treatment. (Weight gain was used as a scale to evaluate the benefit of behavioral therapy.) This finding suggests that behavioral therapy is extremely effective in treating anorectic behavior. What behavioral therapy does is change the setting and alter the contingencies of reinforcement that prompt the individual to exhibit anorectic behavior.

Currently, the behavioral approach has not yet recognized physical activity as a primary characteristic of anorectic behavior (Epling & Pierce, 1988). Although social reinforcement is considered pivotal in the initiation and maintenance of anorectic behavior, behaviorists have yet to accept that dieting

and excessive exercise alter physiological systems that may play a role in the onset and perpetuation of this syndrome (Epling & Pierce, 1991).

Biobehavioral Perspective:

Behavior is executed by physiological systems and this same behavior alters peripheral blood nutrients and hormones as well as central neurotransmitters and neuropeptides. These physiological changes then influence further behavior. In this way, self-starvation and excessive exercise alter both the peripheral and central systems involved in the control of body weight and metabolism (Leibowitz, 1992). The self-starvation behavior is then influenced and maintained by the subsequent changes in the physiological systems (Epling & Pierce, 1991). In other words, these physiological changes reinforce the stimulus which is food deprivation. Mental states are not causal symptoms of self-starvation; rather, these states are by-products of this behavior. Based on this view of self-starvation, Epling, Pierce & Stefan (1983) coined the term "activity anorexia." This term emphasizes the behavior, and not the resultant mental states, produced by self-starvation.

Anorectic behavior results from environmental and physiological determinants. It should therefore be defined and investigated from a biological and behavioral perspective. Epling and Pierce (1988) have combined these perspectives in defining activity anorexia.

Activity anorexia can be defined as a cyclic sequence of events initiated by decreased food intake resulting in an increase in physical activity. This increased physical activity further reduces food intake, eventually resulting in starvation. This sequence of events develops into a positive feedback cycle that leads to increasingly greater exercise and decreased food intake. This definition suggests that excessive physical exercise abates the reinforcing value of food, which in turn exacerbates the emaciation of the organism.

The importance of restricted food intake and excessive physical activity as these relate to self-starvation was discovered by Epling and associates (1983) in controlled experiments with laboratory animals. They discovered that the process of activity anorexia in rats began when the average daily food consumption was restricted to one 60- or 90-minute meal per day and the animals were allowed continual access to rodent running wheels except for during meal times. Running was not forced; the animals chose to run. Wheel running activity increased daily, peaking at eight or more kilometres a day. At this point, the animals began to self-restrict, ignoring food while further increasing their running. The end result was physical decompensation (Epling et al., 1983). Boer and associates (1989) demonstrated that food intake, rather than body weight, controls running behavior (energy expenditure) in rats. This suggests that food restriction may be the precipitating factor for anorectic behavior.

Extensive empirical studies with laboratory animals have implicated a specific set of symptoms that are observed in human anorectic behavior (Epling & Pierce, 1991; Katz et al., 1986; Kron et al., 1978). Epling and Pierce have gathered evidence that extends the animal model for activity anorexia to human behavior. According to their studies, there are seven levels of evidence that support functional similarities between laboratory animals and humans exhibiting anorectic behavior (Epling & Pierce, 1991).

1. ***Physical activity is associated with anorexia in humans as well as laboratory animals.***

   Research has demonstrated that excessive physical activity is a primary characteristic of activity anorexia in laboratory animals (Boer, Epling, Pierce & Russell, 1990; Epling & Pierce, 1988; Epling et al., 1983; Routtenberg & Kuznesof, 1967; 1968). This characteristic is also central to most cases of human anorexia (Beumont, 1983; Casper, Schoeller, Kushner, Hnilicka & Trainer-Gold, 1991; Katz, 1986; Kron et al., 1978).

2. ***Physical exercise reduces food intake.***

   Various studies on metabolism and nutrition suggest that food intake is modulated to a degree by physical exercise. Physical exercise

decreases food intake. This is true of anorectic persons who, for the most part, are energetic (Casper et al., 1991) and exhibit high levels of physical activity despite food restriction (Crisp, 1980; Epstein, Masek & Marshall, 1978; Katz, 1986; Gull, 1874). Brouns and associates (1989) studied a large group of competitive cyclists to determine the effects of intensive exercise on appetite and food consumption. They reported that intensive exercise suppressed appetite and food consumption. It was expected that food intake would increase during the evening following intensive exercise to compensate for energy expended. This compensative food intake did not occur until well after excessive energy expenditure (Brouns et al., 1989). This suggests that intense exercise has an antagonistic effect on food intake. However, when physical activity subsides, food intake normalizes (Epling & Pierce; Tokuyama, Saito & Okuda, 1982).

Food restrictive behavior is also paralleled in laboratory animals. Research has demonstrated that rats will voluntarily restrict food intake when forced to exercise moderately, as compared to sedentary controls (Rivest & Richards, 1990).

3. Decreased food intake increases physical activity.

Physical inactivity has long been associated with increased food consumption. In studies of obese humans, inactivity was concomitant with increased food intake. High caloric diets are associated with inactivity in obese children and adults (Bloom, 1967; Muecke, Simons-Morton, Huang & Parcel, 1992). Muecke and associates (1992) found that children who overeat also under-exercise and that these factors have a synergistic effect for childhood obesity. In contrast, when humans restrict their food intake, they increase their physical activity and their body weight decreases. Keys and associates (1950) conducted a human starvation experiment in which they placed 36 men on a semi-starvation diet and observed their behavior. Although it was reported that the men were inactive, this finding may have been confounded, as the subjects were required to participate in a moderate exercise program. The researchers, however, did note that "...some men exercised deliberately at times. Some of them attempted to lose weight by driving themselves through periods of excessive expenditures of energy..." (Keys et al., 1950:828).

Lower food consumption also increases physical activity in rats. Rats restricted to one 90-minute meal per day and allowed free access to an exercise wheel will spontaneously increase their physical activity

to a point where the organism starts to decompensate (Epling & Pierce, 1984; Epling et al., 1983). Within three days, rats placed on this protocol will self-restrict their food intake while exponentially increasing wheel running activity (Epling & Pierce, 1984). Sedentary animals restricted to a 90-minute meal consume 12-15 g per day of food. After an initial adjustment, these animals adapt and will remain healthy indefinitely. Sedentary animals on ad libitum food will consume 22-25 g per day of food. By restricting the animals' food to 15 g per day, Russell and co-workers (1987) were able to induce voluntary wheel running in rats. After inducing and stabilizing wheel running activity in rats with this altered protocol, Boer (1989) titrated the food allotment in one-gram increments. When the rats' food was decreased by one gram, exercise increased, and, when food increased by one gram, exercise decreased. This suggests that physical activity is modulated by food intake.

4. ***Anorectic behavior in humans is initiated in a pattern similar to what is observed in laboratory animals.***

The primary characteristics of human anorectic behavior, chaotic dieting and excessive exercise, occur early in the onset of the disorder. Beumont and associates (1983) interviewed 25 anorexic patients to

identify and determine the sequential order of symptoms common to the disorder. They reported that chaotic dieting and increased physical exercise were common in all patients interviewed and that these symptoms occurred early in the onset of this syndrome. In addition, chaotic dieting in adolescents and young adults is implicated in initiating a downward sequence of internal events whereby starvation attenuates appetite (Gold & Halmi, 1989). This behavior is patterned in Epling and Pierce's animal model for activity anorexia.

5. ***In humans, psychological symptoms follow rather than precede starvation in anorectic behavior.***

Subjective thoughts, feelings, and beliefs are byproducts of behavior, and these cognitive processes are maintained in part through contingencies of reinforcement as well as changes to "physiological systems, including effectors, receptors, nerves and the brain" (Skinner, 1976:151). This has been demonstrated by empirical studies of neuroendocrine abnormalities induced by starvation.

Glucocorticoids modulate functional processes in the central nervous system involved in information processing and perception (Henkin, 1975). Increased levels of the glucocorticoid, cortisol, have been found in anorectic patients (Pirke & Ploog, 1986). Cortisol is a

mediator of physiological stressors such as hyperactivity and dieting (Gold & Halmi, 1989). These abnormal levels of cortisol resulting from chronic or intermittent food restriction have been linked to distorted thought processes and dysphoria (Laessle, Fischer, Fichter, Pierke & Krieg, 1990). The neuroendocrine abnormality that modulates central cognition results from starvation—it does not precede it (Fichter & Pirke, 1990). A parallel increase in corticosterone (the glucocorticoid having the same functional role as cortisol in humans) resulting from food restriction has also been found in rats (Pirke & Spyra, 1982).

6. ***Disturbances in the diurnal pattern of sleep-wakefulness have been reported in humans and rats exhibiting anorectic behavior.***

Fragmented sleep patterns have been reported in EEG studies on low-weight anorectics, especially during the last four hours of an eight-hour sleep cycle (Lacey, Crisp & Kalucy, 1976). These disturbances in sleep patterns may be the result of decreased levels of L-tryptophan (a precursor of 5-HT) that have been reported in patients diagnosed with anorexia nervosa (Leibowitz, 1990). Low levels of tryptophan are associated with depression and insomnia (Schneider-Helmert & Spinweber, 1986). When insomniacs are treated with L-tryptophan, both sleep latency and total sleep time are improved (Schneider-

Helmert, 1981). Tryptophan levels normalize upon weight restoration, suggesting it is an effect of starvation behavior (Leibowitz,1990). Disruption of the normal diurnal sleep-wakefulness cycle in human anorectics is also paralleled in the food-restricted animal.

Food deprivation in laboratory animals also causes shifts in the diurnal sleep-wakefulness cycle. Rats given free access to rodent running wheels and placed on the classic 90-minute meal protocol inducing activity anorexia exhibit a breakdown in this diurnal pattern. Rats are nocturnal and are inactive in the light phase; however, when subjected to the classic activity anorexia protocol with 12 hours of light in a 24-hour light:dark cycle, they show extreme phase-shifted running activity, choosing to run between 19 and 21 hours a day. Animals in the same experimental condition, but given ad libitum food, run between 10 and 14 hours a day. These results demonstrate the disintegration of the normal diurnal sleep-wakefulness cycle (Morse, Wood, Epling, Pierce & Russell, 1993).

7. ***Endocrine abnormalities resulting from anorexia nervosa disrupt reproductive functions in humans and laboratory animals.***

A minimum body composition of fatty tissue is required to achieve and maintain normal reproductive functions. In humans, chaotic dieting

that reduces fatty tissue below 22% is associated with impaired gonadotropin secretion (Fichter, 1992). In females, insufficient ovarian stimulation and oligomenorrhea or amenorrhea are characteristic of this impairment, while loss of spermatogenesis is common in males (Fichter, 1992; Kuderling, Dorsch, Warnhoff & Pirke, 1984). Chaotic dieting is a physiological stressor that stimulates the production of corticotrophin-releasing hormone (CRH) (Gold & Halmi, 1989). Increased CRH inhibits luteinizing-releasing hormone (LRH) released from the median eminence of the hypothalamus (Rivier & Vale, 1984). Impairment of gonadotropin hormone releasing hormone (GHRH), also called luteinizing hormone-releasing hormone (LHRH), was directly attributed to dieting and weight loss (Pirke, Philipp, Schweiger, Broocks & Wilkens, 1992). LHRH stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). When LHRH levels are reduced by chaotic dieting, LH and FSH levels are also reduced. FSH and LH control the growth of the gonads as well as their function (Ganong, 1991). Reproductive disturbances can therefore be attributed to weight loss resulting from chaotic dieting and excessive exercise.

The reproductive abnormalities observed in anorectic humans are in accordance with data from food-restricted rats. Reduced food intake inhibits LH and FSH, resulting in anestrus in female rats (Watanabe,

Hara & Ogawa, 1992) and a decrease in serum and testicular testosterone levels in male rats (Badger, Lynch & Fox, 1985).

CONCLUSION

Based on the above evidence, the animal model of activity anorexia mimics the core symptoms found in the human condition, providing an investigative tool to further our understanding of the environmental conditions and physiological systems, or the combination of these systems, involved in anorectic behavior. Until now, it has been difficult, if not impossible, to determine whether changes in the environment or in the central or peripheral physiological systems precede, accompany, or follow anorectic behavior. The development of the animal model for activity anorexia provides a strategy for scrutinizing the etiology of this behavior. Before investigating the central and peripheral physiological systems involved in anorectic behavior, a comprehensive study of the effects of food restriction on the diurnal pattern of exercise will be necessary. This animal model, coupled with a non-obtrusive electronic monitoring device, will enable a thorough scientific evaluation of the diurnal pattern of activity exhibited by rats in various protocols of activity anorexia.

Activity anorexia may be best described as an addiction resulting from chronic hyperstimulation of the endogenous opioid system. Endogenous opioids

released as a consequence of dieting and exercise may reinforce and perpetuate self-starvation. Tolerance resulting from chronic stimulation of the opioid system may be countered by a further reduction in food intake and a concomitant increase in locomotor activity. This paradoxical relationship between food intake and exercise culminates in a self-destructive condition. The ability to manipulate and precisely measure the resultant diurnal pattern of wheel running activity exhibited by food-deprived rats offers the possibility of elucidating the physiological mechanisms underlying activity anorexia.

References

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised). Washington, DC: Author.

Badger, T. M., Lynch, E. A., & Fox, P. H. (1985). Effects of fasting on luteinizing hormone dynamics in the male rat. *Journal of Nutrition* 6: 788-797.

Beumont, P. J. V., Abraham, S. F., & Simson, K. G. (1981). The psychosexual histories of adolescent girls and young women with anorexia nervosa. *Psychiatric Medicine* 11: 131-140.

Beumont, P. J. V., Booth, A. L., Abraham, S. F., Griffiths, D. A., & Turner, T. R. A. (1983). Temporal sequence of symptoms in patients with anorexia nervosa: A preliminary report. In P. L. Darby, P. E. Garfinkel, D. M. Garner, and D. V. Coscina (eds.), *Anorexia Nervosa: Recent Developments in Research* (pp. 129-136). New York: Alan R. Liss.

Blaney, N. T. (1985). Eating disorders: Obesity and anorexia. In N. Schneiderman and J. T. Tapp (eds.), *Behavioral Medicine: The Biopsychosocial Approach.* New Jersey: Lawrence Erlbaum Associates

Blindor, B. J., Freeman, D. M. A., & Steinkard, A. J. (1970). Behavior therapy of anorexia nervosa: Effectiveness of activity as a reinforcer of weight gain. *American Journal of Psychiatry* 126: 1093-1093.

Bliss, E. L., & Branch, C. H. H. (1960). Anorexia Nervosa: Its History, Psychology, and Biology. New York: Hoeber.

Bloom, W. L. (1967). Obesity and energy expenditure. *Journal of the Medical Association of Georgia* **56**(9): 381-382.

Boer, D. P. (1989). *Determinants of Excessive Running in Activity Anorexia.* Unpublished doctoral dissertation, University of Alberta, Alberta.

Boer, D. P., Epling, W. F., Pierce, W. D., & Russell, J. C. (1990). Suppression of food deprivation-induced high-rate wheel running in rats. *Physiology and Behavior* **48**: 339-342.

Branch, A., & Zurman, L. (1980). Social attitudes towards patients with anorexia. *American Journal of Psychiatry* **137**: 632-633.

Brouns, F., Saris, H. M., Strouken, J., Beckers, E., Thyssen, N. J., & ten Hoor, F. (1989). Eating drinking and cycling: A controlled Tour de France simulation study, Part I. *International Journal of Sports Medicine* **10**: S32-S40.

Casper, R. C., Schoeller, D. A., Kushner, R., Hnilicka, J., & Trainer-Gold, S. (1991). Total daily energy expenditure and activity level in anorexia nervosa. *American Journal of Clinical Nutrition* **53**: 1143-1150.

Crisp, A. H. (1980). *Let Me Be.* London: Academic Press.

Dally, P. (1967). *Anorexia Nervosa.* London: William Heinemann Medical Books.

Dally, P., Gomez, J., & Isaacs, A. J. (1979). *Anorexia Nervosa.* London: William Heinemann Medical Books.

Epling, W. F., & Pierce, W. D. (1984). Activity-based anorexia in rats as a function of opportunity to run in an activity wheel. *Nutrition and Behavior* **2**: 37-49.

Epling, W. F., & Pierce, W. D. (1988). Activity-based anorexia: A biobehavioral perspective. *International Journal of Eating Disorders* **7**: 475-485.

Epling, W. F., & Pierce, W. D. (1991). Solving the Anorexia Puzzle: A Scientific Approach. Toronto: Hagrefe and Haber.

Epling, W. F., Pierce, W. D. & Stefan, L. (1983). A theory of activity-based anorexia. *International Journal of Eating Disorders* **3**: 27-46

Epstein, L. H., Masek, B. J., & Marshall, W. R. A. (1978). A nutritional based school program for control of eating in obese children. *Behavioral Therapy* **9**: 766-778.

Fichter, M. M. (1992). Starvation-related endocrine changes. In K. A. Halmi (ed.), *Psychobiology and Treatment of Anorexia Nervosa and Bulimia Nervosa.* London: American Psychiatric Press.

Fichter, M. M., & Pirke, K. M. (1990). Endocrine dysfunction in bulimia nervosa. In M. M. Fichter (ed), *Bulimia Nervosa: Basic Research, Diagnosis and Therapy* (pp. 235-257). Wiley, Chichester.

Freud, S. (1954). *The Origins of Psychoanalysis: Letters to Wilhelm Fliess, Drafts and Notes: 1887-1902.* M. Bonaparte, A. Freud, and E. Keis (eds.) (E. Mosbacher and J. Strachey, trans.). New York: Basic Books.

Ganong, W. F. (1991). *Review of Medical Physiology*. California: Appleton and Lange.

Garner, D. M., & Garfinkel, P. E. (1987). Socio-cultural factors in the development of anorexia nervosa. *Psychological Medicine* **10**: 647-656.

Gold, P. W., & Halmi, K. A. (1989). Affective and eating disorders: Appetite, weight regulation, and neuroendocrine function. *Psychopharmacology Bulletin* **25**(3): 433-438.

Gull, W. (1874). Anorexia nervosa (apepsia) hysteria, anorexia hysteria. *Transcripts of the Clinical Society, London* **7**: 22-31.

Halmi, K. A. (1985). Behavioral management for anorexia nervosa. In D. M. Garner and P. G. Garfinkel (eds.), *Handbook of Psychotherapy for Anorexia Nervosa and Bulimia.* New York: Guilford Press.

Henkin, R. I. (1975). The role of adrenal corticosteroids in sensory process. In R. O. Greep and E. P. Astwood (eds.), Handbook of Physiology (pp. 209-230).

Janet, P. (1903). Obssessions et la Psychasthénie (Vols. 1 and 2). Paris: Felix Alcan.

Katz, J. L. (1986). Long-distance running, anorexia nervosa, and bulimia: A report of two cases. *Comprehensive Psychiatry* **27**(1): 74-78.

Keys, A., Borzek, T., Henschel, A., Mickelson & Taylor (1950). *The Biology of Human Starvation.* Minneapolis: University of Minnesota.

Kron, L., Katz, J. L., Gozynski, G., & Weiner, H. (1978). Hyperactivity in anorexia nervosa: A fundamental clinical feature. *Comprehensive Psychiatry* **19**(5): 433-440.

Kuderling, I., Dorsch, G., Warnhoff, M., & Pirke, K. M. (1984). The action of prostaglandin E2, naloxone and testosterone of starvation-induced suppression of luteinizing hormone-releasing hormone and luteinizing hormone secretion. *Neuroendocrinology* **39**: 530-537.

Lacey, J. (1982). Anorexia nervosa and a bearded female saint. *British Medical Journal* **285**: 1816-1817.

Lacey, J. G., Crisp, A. H., & Kalucy, R. C. (1976). Study of EEG sleep characteristics in patients with anorexia nervosa before and after restoration of matched population mean weight consequent on ingest of a "normal" diet. *Postgraduate Medical Journal* **52**: 45-49.

Laessle, R. G., Fischer, M., Fichter, M. M., Pirke, K. M., & Kreig, J. C. (1992). Corticol levels and vigilance in eating disorder patients. *Psychoneuroendocrinology* **17**(5): 475-484.

Lasèque, C. (1873). On hysterical anorexia. *Medical Times and Gazette* **2**: 265-266, 367-369.

Leibowitz, S. (1992). Neurochemical-neuroendocrine systems in the brain controlling macronutrient intake and metabolism. *Trends in Neuroscience* **53**(3): 242-244.

Leibowitz, S. F. (1990). The role of serotonin in eating disorders. *Drugs* **39**(Suppl. 3): 33-48.

Lucas, A. R., Beard, M. C., O'Fallon, W. M., & Kurland, L. T. (1991). 50-year trends in the incidence of anorexia nervosa in Rochester, Maine: A population based study. *American Journal of Psychiatry* **148**(7): 138-147.

Minuchin, S., Rosman, B. L., & Baker, L. (1978). *Psychosomatic Families: Anorexia Nervosa in Context.* Mass: Harvard University.

Morse, A. D., Wood, G. O., Epling, W. F., Pierce, W. D., & Russell, J. C. (1993). Diurnal pattern of wheel running activity in the rat: Effects of food deprivation in activity anorexia. (Unpublished results.)

Morton, R. (1694). *Phthisiologica: Or a Treatise of Consumptions.* London: Smith and Walford.

Muecke, L., Simons-Morton, B., Huang, I. W., & Parcel, G. (1992). Is childhood obesity associated with high fat foods and low physical activity. *Journal of School Health* **62**(1): 19-23.

Pirke, K. M., Philipp, E., Schweiger, U., Broocks, A., & Wilkens, T. (1992). Neuroendocrine and reproductive functions. In: K. A. Halmi (ed.), *Psychobiology and Treatment of Anorexia Nervosa and Bulimia Nervosa* (pp. 151-167). London: American Psychopathological Association Series

Pirke, K. M., & Ploog, D. (1986). The psychobiology of anorexia nervosa. In R. J. Wurtman and J. J. Wurtman (eds.), *Nutrition and the Brain* (Vol. 7) (pp. 167-198). New York: Raven Press.

Pirke, K. M., & Spyra, B. (1982). Catecholamine turnover in the brain and the regulation of LH and corticosterone in starved male rats. *Acta Endocrinology* **100**: 168-176.

Rivest, S. and Richards, D. (1990). Hypothalamic paraventricular nucleus lesions do not prevent anorectic effect of exercise in male rats.

Rivier, C., & Vale, W. (1984). Influence of corticotrophin releasing factor on the reproductive function in the rat. *Endocrinology* **114**: 914-921.

Routtenberg, A., & Kuznesof, A. (1968). Self-starvation of rats living in activity wheels: Adaptation effects. *Journal of Comparative Physiology and Psychology* **66**: 234-238.

Routtenberg, A., & Kuznesof, A. W. (1967). Self-starvation in rats living in activity wheels on a restricted feeding schedule. *Journal of Comparative and Physiological Psychology* **64**: 414-421.

Russell, G. F. M. (1970). Anorexia nervosa: Its identity as an illness and its treatment, In J. K. London (ed.), Modern Trends in Psychological Medicine (pp. 131-164). Butterworth.

Russell, J. C., Epling, W. F., Pierce, W. D., Boer, D. P., & Amy, R. (1987). Induction of voluntary prolonged running by rats. *Journal of Applied Physiology* **63**: 2549-2553.

Schneider-Helmert, D. (1981). Interval therapy with L-tryptophan in severe chronic insomniacs: A predictive laboratory study. *International Pharmacopsychiatry* **16**: 162-173.

Schneider-Helmert, D., & Spinweber, C. L. (1986). Evaluation of L-tryptophan for treatment of insomnia: A review. *Psychopharmacology* **89**: 1-7.

Skinner, B. F. (1976). *About Behaviorism*. New York: Vintage Books.

Strober, M. (1991). Disorders of the self in anorexia nervosa: An organismic-developmental paradigm. In C. Johnsons (ed.), Psychodynamic Treatment of Anorexia Nervosa (pp. 354-373). New York: Guilford Press.

Thoma, H. (1967). *Anorexia Nervosa.* New York: International Universities Press.

Tokuyama, K., Saito, K., & Okuda, H. (1982). Effects of wheel running on food intake and weight gain of male and female rats. *Journal of the Medical Association of Georgia* **28**(5): 899-903.

Watanabe, K., Hara, C., & Ogawa, N. (1992). Feeding conditions and estrous cycle of female rats under the activity stress procedure from aspects of anorexia nervosa. *Physiology and Behavior* **51**: 827-832.

Yates, A. (1990). Current perspectives on eating disorders: Treatment, outcome and research directions. *Journal of the American Academy of Child and Adolescent Psychiatry* **29**(1): 1-9.